

THE RELEVANCE OF PRE-MORBID COGNITIVE  
IMPAIRMENT TO SCHIZOPHRENIA.

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## Abstract

This thesis begins with an exploration of the historical associations between learning disability and schizophrenia, which leads to the modern supposition that schizophrenia is commoner in people with learning disability than the normal population. A critical evaluation of both community and hospital epidemiological studies indicates that the point prevalence of schizophrenia in people with mild learning disability is around 3% i.e. around three times that expected in the normal population. Five possible mechanisms to account for this increase are postulated and discussed: a chance co-occurrence, a common aetiology, an epiphenomenon, a severe schizophrenia and a '*de novo*' disease.

A case controlled study which aims to characterise the nature of schizophrenia in people with pre-morbid mild learning disability is described. Index subjects with schizophrenia and pre-existing mild learning disability (co-morbidity), were identified from a national database. Two age and sex-matched control groups were identified from local case registers, the first with a diagnosis of schizophrenia, but no pre-morbid cognitive impairment, the second with mild learning disability, but no history of psychosis. A total of 101 subjects were seen on several occasions to complete the protocol, case notes were reviewed, and where possible interviews with relatives and carers were conducted. Blood was taken for karyotypic analysis from co-morbid subjects. The results of the study and their significance are discussed in chapters



dealing individually with sociodemographic, clinical, memory, neurological, adaptive behaviour and genetic variables.

The five mechanisms postulated to account for the increased point prevalence of schizophrenia in people with mild learning disability are reconsidered in light of the findings of this study. It is suggested that the mechanisms are not mutually exclusive. However, evidence is presented to support the possibility that the co-morbid population may, in some cases, represent a severe form of schizophrenia, which may be of genetic aetiology. Finally, the importance of further study of the co-morbid group is emphasised. In the future, such study may provide important clues as to the genetic origins of the psychoses, and widen our understanding of schizophrenia.

### Declaration

I , Dr Gillian A. Doody declare that I have composed the work contained in this thesis. The research presented here was all conducted whilst I was in post in South East Scotland. I conducted this research myself, except where due acknowledgement has been given to others. I have not submitted this thesis in candidature for any other degree, diploma or professional qualification.

Signed:

Date: 15<sup>th</sup> May 1998

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Dr Tracy Sanderson was appointed a Wellcome Fellow in 1996 to perform cerebral MRI scans on the study population and assisted by performing a relatively small number of subject ratings and case note reviews. The author performed the majority of all subject ratings. Ms Cathy McLeod was appointed as a research assistant on this project for 18 months. She was involved in clerical aspects of the study and accompanied the author on visits to subjects at home for both ethical and safety reasons. She also conducted the Vineland Assessments with carers, relatives or friends of subjects in less than 50% of cases. I am grateful to both Dr Sanderson and Ms. McLeod for their contributions to this study.

Professor Chris Frith advised on the use of the Vineland Adaptive Behaviour Scales and also on the Quick IQ Test and NART. Mr Paul Dickens taught me

to use the Vineland Scales, Dr Ronan O'Carroll advised on the use of the RBMT and Dr Cunningham Owens on the use of the AIMS, TAKE and DISCUS.

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A dissertation derived from the first three chapters of this thesis entitled "Schizophrenia and mild learning disability: an historical and epidemiological re-appraisal" was awarded the Brian Oliver Prize of the Royal College of Psychiatrists in 1997

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*"The emotional life of idiots deviates from the normal almost as widely as their intelligence ..... it would seem likely that a careful study of the type and degree of these deviations might throw light not only on the emotional life of the idiot himself but upon those of mankind in general. ... If this be so, one might expect to find amongst idiots larval or primitive prototypes of the emotional abnormalities, the psychoses and psychoneuroses of the intellectually normal."*

C.J.C. Earl (1934)

## PART ONE

### CHAPTER ONE

#### LEARNING DISABILITY AND SCHIZOPHRENIA -

##### AN HISTORICAL PERSPECTIVE.

*"Understanding and creativity in psychiatry may be enhanced by a knowledge of its history"*

G. Berrios (1992)

#### 1.1 The social conceptualisation of mental illness and learning disability prior to 1800.

In prehistoric times (circa 7,000 B.C.) our ancestors lived predominantly in nomadic tribes and frequently undertook long marches in search of food and shelter. Infants with disease, deformity, those orphaned at birth or those born illegitimately, were problematic on such journeys (Durant, 1935). Despite crude attempts to rectify obvious cranial imperfections, as evidenced by skull fragments found on the Danish peninsula of Jutland indicating that trephination had been performed on a hydrocephalic infant (Harms, 1976), infanticide was commonplace.

As a political structure gradually evolved, so too did laws, religions and a slave based economy. Infanticide was criminalised by the Egyptians around 2850 B.C., the punishment being that the mother should hug the dead child for three days and nights (Scheerenberger, 1983).



In Mesopotamia between 1700 and 560 B.C. the building blocks of modern day society were gradually emerging, but the society here was not so advanced as Egypt. Although inventions, such as the wheel and pulley, led to social cohesiveness and common purpose, mental disease or disability resulted in a loss of manpower

Contemporaneously, the ancient Greeks rigidly reinforced old ideals, despite the relative precociousness of their societal structure. Aristotle (384-322 B.C.) stated 'As to the exposure and rearing of children, let there be a law that no deformed child shall live.' This was taken literally in the cities of Sparta and Athens. In Sparta, only the strongest and brightest citizens were allowed to have children and infanticide was mandatory for any birth deformity. There was believed to be little value in book learning, as strength and battle skills were the qualities every male child strove for. Children were removed from their parents at the age of seven to attend military academies, here the emphasis was on a barrack room lifestyle in preparation for warfare. This ethos is best illustrated by census data from 300 B.C. Athens. The death rate exceeded the birth rate (Scheerenberger, 1983) and only one family in every hundred was permitted to rear more than one female child.

Hippocrates (460-370 B.C.) is largely credited with the first distinct description of mental handicap. He utilised the theory of four humors (blood, phlegm, yellow and black bile) to categorise the condition stating it was the result of 'sluggish black bile' (Scheerenberger, 1983). He also described microcephaly,

craniostenosis and latterly epilepsy which he attributed to 'the blockage of passage of phlegm from the brain' (Hill, 1981).

The Roman Empire was founded upon a patriarchal family structure. In the Second Century A.D. deformed children were further mutilated to make them better beggars and a market was established where citizens might purchase 'legless, armless, 3-legged men, giants, dwarfs or hermaphrodites' (Scheerenberger, 1983). The gradual advent of Christianity abolished such practices and by the Fourth Century A.D. the Romans came to consider infanticide as a despicable crime.

In the early middle ages, the first attempts at containing the mentally impaired were made. Foundling homes and orphanages were established in European Cities. Care was generally poor and many residents died. The Bethlem Hospital was established in London in 1377, following a bequest of land to the Church of Bethlem by the Sheriff of London in 1247. A voyeuristic fascination slowly perpetrated the establishment. At Bethlem, paying guests viewed inmates, who were not kept as resident for longer than a year to ensure that visitors returned. The kudos of a sight-seeing visit to the hospital gradually became second only to visiting lions kept at the Tower of London and by the 17th Century Bethlem was the Capital's busiest tourist attraction (Porter, 1990).

The publication of *Malleus Maleficarum* (Trans: The Witch's Hammer) in 1487 led to the inquisition. During this dark historical period it was believed that, 'if

the patient can be relieved by no drugs, but rather seems to be aggravated by them, then the disease is caused by the devil' - no mentally impaired person was therefore exempt from being branded a witch or accused of having occult connections. The astronomer Tycho Brache (1546-1601) was known to keep a dwarf named 'Zep' as a companion, 'an imbecile to whose mutterings the astronomer listened to as divine revelations' (Kanner, 1964).

The 17th and 18th centuries heralded the age of 'enlightenment and reason'. Although conflict and plague engulfed Europe and many hardships were endured by the population, the advent of the industrial revolution brought with it hope and employment. Medicine emerged from its enigmatic shroud and new discoveries genuinely advanced practice and treatment. The paediatrician Robert Pennel published a textbook containing a lengthy review of epilepsy suggesting 45 possible treatments. Walter Harris (1647-1732) made observations on the mechanism of hereditary; 'let those who prefer a strong, vigorous and healthy offspring before money, take care to avoid epileptic, scorphulous and leprous mothers' (Ruhräh, 1925).

The respected physician and anti-Aristotelian philosopher, John Locke contributed significantly to the field in 1690. He believed that distinct species exist only to the extent that the human race have ideas of and names for them (Goodey, 1995). Reflecting on the distinction between that which we now regard as mental illness and learning disability he stated; 'herein seems to lie the difference between idiots and madmen. That madmen put wrong ideas

together and reason from them, but idiots make very few or no propositions and reason scarce at all' (Doll, 1962). This simple statement paved the way for the social diversification of the two conditions.

The century that followed saw a magnification of the distinction between the two conditions and embedded both into the medical domain. The impetus for this was the publication in 1800 of the Edinburgh based physician William Cullen's nosology of diseases. Here he described, under the class II neuroses, the "Versaniae" or 'lesions of the judging faculty without fever or coma' (Cullen, 1800). Such afflictions were further sub-divided into amentia (either congenital, senile or acquired), melancholia, mania and oneirodynia.

## 1.2 A brief historiography of learning disability 1800 - 1945.

The reformist fervour of Victorian Britain brought with it an ethos of treatability to the care of those with mental impairment. The earliest Nineteenth Century evidence of such philanthropy was provided by the Frenchman Jean Itard (1774-1838). Itard sought to locate and 'treat' the wild boy of Aveyron, he subsequently named the captive boy Victor in 1802. Phillipe Pinel decreed that the boy's 'wildness' was a fake and that he was 'an incurable idiot, inferior to domestic animals' (Kanner, 1964). However Itard persevered with Victor's education programme for five years. The ultimate failure of his venture, which resulted in the death of the latterly institutionalised Victor in his early twenties, was concealed from the media of the day. The scientific community praised

Itard's achievements and hailed his rehabilitative programme as a breakthrough in the treatment of idiots (Lane, 1977).

Esquirol admired and further advanced the work of Itard. This led him to challenge the prevailing view that idiocy was a disease. In direct opposition to earlier work by Pinel, Esquirol wrote; 'idiocy is not a disease but a state in which the intellectual faculties are never manifested or developed for lack of education' (Esquirol, 1838). Itard's pupil Onésime Édouard Séguin also adhered to Esquirol's belief, he established a training school for idiots and imbeciles at the Bicêtre Hospital in Paris in 1837 (Day and Jancar, 1991). He further medicalised the care of idiots by producing a seminal textbook on their 'modern day education' (Séguin, 1846) in which he introduced the term 'psycho-physiological training'.

Further afield, in the Swiss Alps, it had been observed from the late sixteenth century that certain valleys had a higher than expected rate of cretinism, for which there was no scientific explanation (Cranefield, 1961). Johann Jakob Guggenbuhl (1816-1863) obtained land near Interlaken at Abendberg and established an institution for the care of children with cretinism in 1842 (Kanner, 1959). The emphasis of the school was on physical exercise, a good diet and training to develop the sensory systems (Miller, 1995). The regime at Abendberg quickly gained international acclaim. Many visitors flocked to see the 'cured' children and similar institutions gradually emerged throughout Europe and the U.S.A.

The author Charles Dickens visited Abendberg in 1853 and subsequently published an article praising its innovative treatment approach (Dickens, 1853). Other travellers to Abendberg included the philanthropist Andrew Reed, who subsequently founded the first 'Asylum for Idiots' in Highgate, London, and the Misses White who opened the first British school for imbecile children at Bath in 1846 (Day and Jancar, 1991).

Esquirol, was further inspired by the work of Guggenbuhl, and continued his propagation of both Itard and Séguin's ideas publishing his frequently quoted work, *Mental Maladies* in 1845. In this he stated; 'A man in a state of dementia is deprived of advantages which he formerly enjoyed: he was a rich man who had become poor. The idiot, on the other hand, has always been in a state of want and misery' (Esquirol, 1845). The work was not without its critics, typical of these was Henry Monro (Scull, 1993). Monro believed that 'to divide one sort of dementia from another - to go to the length Mr Esquirol has ..... is curious rather than useful' (Monro, 1850).

However, Abendberg's fame was to be tarnished following a formal complaint lodged by the British Minister to Berne in 1858. This launched an official inquiry led by two Swiss physicians, Vogt and Verdat, into the practices at the institution. Guggenbuhl was abroad at the time of their visit, lecturing on his new techniques occupied the majority of his time, and he became a rare sight in Abendberg. Their report concluded that no 'cures' had ever been achieved

(Miller, 1995) at Abendberg and disillusioned many of those physicians who had been carried along by Guggenbuhl's wave of therapeutic optimism. Nevertheless, Guggenbuhl's legacy was to kindle a spark which resulted in an era of institutional expansion (Kanner, 1964) throughout the western world.

As more and more institutions became established in England and Wales, the nineteenth century literature filled with reports of concern over increasing numbers of idiots. The number of patients in specific idiot asylums rose from 400 in 1864 to 2,000 in 1914. However, these figures represented only the tip of the proverbial iceberg, the majority of idiots were housed in other public institutions, such as workhouses, or asylums for the insane. The total number of idiots in England and Wales was estimated at 29,452 in 1881 (Ryan and Thomas, 1994). Hence the specialised institutions housed only around 3% of the mentally handicapped population. The introduction of the 1886 Idiots Act sought to rectify this situation by empowering local authorities to build special asylums for idiots, thus firmly establishing the division between mental illness and mental handicap.

The rise of the asylum shifted the care of the mentally handicapped into the public domain, further medicalising the condition and attempting to produce an ordered, model societal structure for the socially incompetent. Whether the ethos of institutional philanthropy, or society's wish to dispose of its undesirable elements motivated the rise of the asylum is debatable (1992). At one extreme



Scull (1993) states; 'asylums were largely receptacles for the confinement of the impossible, the inconvenient and the inept.'

The social tide had now turned once again, the transformation being fuelled by the publication of Benedict Morel's theory of degeneracy (1857), the exposure of false therapeutic claims at Abendberg, and the gross overcrowding seen in the asylums.

Morel (1809-1873) had spent 10 years of his childhood living in a monastery and based his theory on man's original sin against God, as described in the book of Genesis (Beer, 1996). He described the concept of 'transformational heredity', or 'polymorphic heredity', whereby man became prone to physical and mental disabilities which could be either acquired or congenital. In the hereditary case the theory stated that the disability would follow a downward or degenerative path to further deterioration through successive generations. In today's terms it could be argued that Morel was the first physician to describe the molecular genetic phenomenon we recognise as 'anticipation'. At the time Morel's theory was in contradistinction to that of Darwin, who published the 'Origin of the Species' in 1859.

The conclusions drawn from Gregor Mendel's gardening experiments in 1868 provided scientific evidence of heredity models and as a result transgenerational studies came into vogue. Morel's pupil, Valentin Magnan (1835-1916), refined his mentor's original hypothesis to fit evolutionary



terminology and dispensed with its religious components. Magnan stated that although man naturally strived to attain a higher evolutionary form, it was inevitable that some individuals would fall by the wayside if they were unable to successfully adapt to life's demands.

John Langdown Down (1828-1896) published his 'observations on an ethnic classification of idiots' in the Journal of Mental Science in 1867. His work being made possible by the aggregation of large numbers of idiots in specialised institutions. In this now classic paper he not only defined the clinical characteristics of 'Down's Syndrome' by use of analogy to the distinguishing features of the Mongoloid race, but also described other ethnic features in individuals in his institution with intellectual impairments i.e. Ethiopian, Malay, Negroid and Aztec. The latter group were defined by a characteristically small head circumference (Down, 1867). Down's observations were largely ignored by his colleagues at the time of first publication, although they epitomised the prevailing degeneracy theory. However, his idea of delineating an aetiological classification system was to be seized by upon by William Ireland (1832-1909), a decade later.

Between 1869 and 1879, Ireland was Superintendent of the Scottish National Institution for Imbecile Children at Larbert, Central Scotland. His book, 'On Idiocy and Imbecility', published in 1877, is widely regarded as the first well-organised and medically orientated textbook of learning disability (Kanner, 1964). He sought to classify idiocy by aetiological groupings and set out twelve

sub-divisions. Ireland was a believer in the newer heredity views on aetiology, although he rejected degeneracy theories, and stated in his book, 'Idiots frequently are born in families in which there is a decided neurotic tendency, as manifested by the appearance of insanity, imbecility, or epilepsy' (Ireland, 1877). Ireland paved the way for other medically trained textbook writers, such as Shuttleworth and Potts (1895), to explore the subject further.

The introduction of The Education Act in England and Wales in 1870 made public education compulsory for all children. It brought education to the forefront of the reformist agenda, raising the popularity of its inceptor Gladstone, in a volatile political climate. Schools coped with children of all abilities and it soon became clear that basic streaming was necessary, if brighter pupils were to succeed. The Defective and Epileptic Children (Education) Act was therefore passed in 1899. The Act made provision for the education of a group of children who could not be taught adequately in ordinary schools, but who were not sufficiently impaired to be categorised as idiots or imbeciles (Day and Jancar, 1991).

New methods of assessing a child's intellectual potential were now urgently required. The French government commissioned Alfred Binet to find a means of identifying children who were failing in the conventional education system (Thom, 1995). Binet (1905) subsequently developed a battery of test questions which sought to establish a child's mental age, in relation to their chronological peers. In 1908 the German psychologist Stern took Binet's ideas one step

further and utilised the concepts of 'mental age' and 'chronological age' to create a ratio - the intelligent quotient (I.Q.). The concept was adopted on a massive scale from 1914-1918 to identify and reject unsuitable army conscripts, and soon became incorporated into everyday vocabulary.

Meanwhile, a new movement broke into scientific circles throughout Europe - a throwback to the theories of Morel, but now also embracing the new Darwinian concepts. The extremism of the eugenics movement was reflected in the publication of 'The Right to Death' by the German psychologist, Jost in 1895. In this he stated; 'in cases of incurable suffering the State can say its interest and the interest of the person concerned demand equally a quick and painless death, but it must be left to the patient to decide between life and death. In the case of mental patients this right reverts to the State, and the diagnosis of incurability is in itself sufficient to justify killing.' (Meyer, 1988). Suddenly, the diagnostic and prognostic ponderings of the academic psychiatric community over the preceding three decades assumed a darker significance.

The 1913 Mental Deficiency Act in England and Wales introduced compulsory certification of all people admitted to institutions with a diagnosis of mental deficiency. There now existed a registration and administrative system for the identification of both mentally ill and mentally handicapped people. Binding and Hoche published their book 'Permission for the Extermination of Worthless Life' in 1920. The main emphasis of the text was on the need to kill the incurably mentally ill (Mayer, 1988).

By 1926, 23 American States had introduced a law encouraging sterilisation of all mentally defective individuals (Kanner, 1964). In Britain, the Wood Committee and the Brock Committee were convened by parliament to consider the introduction of similar laws in 1928 (Thom, 1995). Very little psychiatric research occurred between 1920 and 1930. Europe was recovering from the political and economic sequelae of the First World War, funding for mental health research was not high on the agenda. However, beliefs in heritability of both intelligence and mental illness were almost universal. By 1929 sterilisation statutes had been instituted in Canada, Denmark, Switzerland and Finland.

The National Socialist Party came to power in Germany in 1933. Within a few months of Hitler taking office as Chancellor the Law for the Prevention of Offspring with Hereditary Diseases was passed. This paved the way for the coercive sterilisation of more than 350,000 people between 1934 and 1939 (Bock, 1986). The categories of perceived hereditary diseases were; feeble-mindedness, schizophrenia, manic-depressive psychosis, epilepsy, Huntingdon's chorea, hereditary blindness, hereditary deafness, 'grave bodily malformation' and hereditary alcoholism. Hereditary Health Courts were established to enforce the law and decide who should be sterilised, they consisted of two physicians, a judge and an administrative Health Officer with strong political ties to the Nazi Party (Lifton, 1986). This legislation marked the beginning of the Nazi regime, in the words of Kanner, 1964; 'The one man

Hitler, who probably would not have come out too badly in terms of the Binet-Simon scale, did more damage than all the mental defectives in history'.

In 1935 Germany passed the Nuremberg Laws which prohibited marriage or sexual contact between Jews and non-Jews. There was promotion of positive eugenics, encouraging large Aryan families and the 'Nazification of medicine' occurred by sweeping reorganisation and restructuring of medical school curricula. Those academic psychiatrists who opposed the changes were deposed, or exiled, they included, Bonhoeffer, Creutzfeldt, Kurt Schneider, Kretschmer and Kleist (Lifton, 1986). By 1936 'impaired children' were being sent to specially designed treatment centres where they were killed by mercurial overdoses. By 1939, the inmates of mental hospitals were being transferred to other specialised centres where they were killed by carbon monoxide gassing. Doctors became reluctant to make diagnoses, due to the implications for patients. In the same year the 'T<sub>4</sub>' extermination programme was initiated using hydrogen sulphide gas. It did not become routinely used in concentration camps until 1941 (Lifton, 1986).

In Britain the reports of the Brock and Wood Committees aroused controversy. The government commissioned Penrose to undertake a large study of the inmates of an institution for the mentally handicapped. The results of the survey (Penrose, 1938), indicated that in the majority of cases the parents of mentally handicapped inmates were not themselves mentally handicapped.

This helped to defuse eugenic fervour in the U.K. Meanwhile the politicians had diverted their attentions to the more pressing issues of World War II.

### 1.3 Schizophrenia before 1900 - fact or fiction?

Prior to the eighteenth century psychopathological accounts are rare. Youseff and Youseff (1996) have argued that case histories encountered in medieval Islamic writings and legends point to the existence of schizophrenia as long ago as the ninth century. Twelfth century descriptions from St. Bartholomew's Hospital in London also exist and reveal four probable cases of schizophrenia (Wilmer and Scammon, 1954). Furthermore, records suggest that the illness of King Henry VI in the fifteenth century was characterised by schizophrenic symptoms (Clark, 1975).

Crichton (1996) provides evidence that clear descriptions of schizophrenic symptomatology may be found in the writings of the German philosopher Immanuel Kant in his book of 1798 entitled 'Pragmatic aspects of anthropology'. However, it is generally accepted that clinically adequate descriptions of schizophrenia first appeared independently in England and France in 1809 (Gottesman, 1991). Elaborations for classification purposes of delusional syndromes were subsequently made by Morel, Kaulbaum, and Hecker. However, Clouston's description of "adolescent insanity" (Clouston, 1888), is regarded by many as the first categorical description of schizophrenia. Although recent work has indicated that what he described was

not comparable to contemporary definitions of the illness (Beveridge, 1995). Nevertheless, Clouston's description pre-dated those of both Kraepelin and Bleuler.

Kraepelin wrote the first three editions of his influential textbook between 1883 and 1889, in these he based much of his early classifications on the work of Griesinger (1876). It was not until the publication of the fifth edition of his textbook in 1896 that Kraepelin first described dementia praecox. This was described in the context of being one of three psychotic conditions, the other two being katatonia and dementia paranoides.

In the sixth edition (1899, English translation 1904), Kraepelin introduced the concept of manic depressive psychosis and distinguished this from dementia praecox in terms of outcome and prognosis. Speculating on the aetiology of dementia praecox, he states; 'It seems probable, judging from the clinical course, and especially in those cases where there has been rapid deterioration, that there is a definite disease process in the brain, involving the cortical neurones' (Beer, 1996).

Bleuler finally coined the term schizophrenia in 1911. There were, however, several fundamental discrepancies between Kraepelin's and Bleuler's descriptions and initially Kraepelin viewed the work of Bleuler with scepticism. Firstly, Bleuler characterised primary and secondary features of the disease, whereas Kraepelin had based his description on general observations and no



specific symptoms had been isolated. Secondly, Bleuler had been influenced by the work of many of the contemporary psychoanalysts, including Freud, Abraham and Jung and therefore incorporated psychoanalytical formulations into his descriptions (Hoenig, 1995). Kraepelin's belief that dementia praecox was a 'disease of cortical neurones' was understandably in conflict with such an analytical approach. Hoff's (1995) comments are concise; 'There are striking parallels between the basic questions of Kraepelin's approach on the one hand and the actual biologically oriented psychiatric research strategies on the other hand. This fact makes the historical research on Kraepelin practically relevant for present-day psychiatry.'

Hare's recency theory (Hare, 1988) suggests that Clouston described some of the very first cases of schizophrenia ever to emerge, and that prior to his reports the disease did not exist. Many authors have contested this view, although relatively few have sought out original historical archives to substantiate their claims (Klaf and Hamilton, 1961; Doody et al, 1996). Moreover, an extensive historical review by Turner (1992), offers compelling evidence in support of an antithetical permanency hypothesis, indicating that schizophrenia is by no means a new disease.

### 1.3 Schizophrenia and pre-morbid cognitive impairment 1900 - present.

#### 1.3.1 Co-morbidity

Kraepelin described the concept of 'pfropfschizophrenia' (translated as 'engrafted schizophrenia') in 1919. He estimated that, based on clinical



observation, around 7% of all cases of dementia praecox arose in individuals with pre-morbid cognitive impairment, or idiocy. He identified other characteristic features of this sub-type of dementia praecox which included, an early age of onset of psychosis, mannerisms, stereotypies, and 'negativistic features' (Turner, 1989). Kraepelin's description of pfpopschizophrenia launched a philosophical debate into the psychiatric literature, which was to exercise the minds of academics for the next 30 years, and remains unresolved today.

Tredgold (1908) maintained that mental illness was 26 times more frequent in the mentally retarded population, than the normal population. Berkley (1915) was more cautious in his claims, but simply complemented Kraepelin's findings by stating that idiots seemed to be more likely to develop psychoses relative to individuals of normal intelligence (Reid, 1989a). However the basic question remained, was pfpopschizophrenia a unique and discrete disease entity, or did it represent a chance co-occurrence of two quite distinct conditions in one individual ?

The work of Berkley added weight to Kraepelin's belief that the former explanation was correct. If the two conditions simply co-occurred, then one would expect the overall point prevalence to be considerably lower than that of either condition in isolation. In addition, there would be no explanation for the increased point prevalence of psychoses in the mentally handicapped population. Kraepelin therefore believed that pfpopschizophrenia was a distinct

sub-type of dementia praecox, the pre-morbid (i.e. pre-psychotic) mental impairment being integral to the disease process per se. Luther (1913) contested this view, maintaining that pfpopschizophrenia was no more than a chance combination of two separate illnesses; schizophrenia and mental deficiency.

Greene published a study of 'developmental stigmata' e.g. cyanosis and head circumference, in 100 feeble-minded patients and 100 patients with dementia praecox, in 1930. He also studied 100 normal controls. Greene concluded that the results from the feeble-minded and dementia praecox subjects were comparable, and quite different from the controls. Therefore, he deduced, that the aetiology of both conditions should be regarded as common and singular. He also provided the first experimental evidence to substantiate this opinion.

Kallman (1941), a pro-eugenic researcher in pre-war America, refuted the ideas of Greene with a large scale family study of the relatives of patients with either schizophrenia or 'feeble-mindedness'. He found no increase in the frequency of mental deficiency in the relatives of schizophrenics, and no increase in schizophrenia in feeble-minded parents. From these results he concluded that 'endogenous forms of schizophrenia and mental deficiency are based on different genetic factors'. Kallman thus concurred with the previous idea of Luther. Today, one might challenge his conclusion by considering the loose definition of schizophrenia employed by Kallman in the pre-operationally

defined era, and also by criticising the study population, which excluded co-morbid probands.

A completely different population was considered by O'Gorman (1954). Inspired by the concept of 'dementia praecocissima' (de Santis, 1906), he postulated that dementia praecox beginning in infancy or childhood could produce a condition of *de facto* mental defect. In order to substantiate his theory, he reviewed the diagnosis of 43 male children, all under the age of 14, residing in the Borocourt Hospital for mental defectives, Oxfordshire. 6 of the 43 boys were considered to be psychotic. These children displayed no evidence of epilepsy, or signs of organic cerebral disease. He forwarded the hypothesis that 'many children diagnosed mentally defective are in reality psychotic, the degree of the defect depending on the severity and the duration of the psychosis'. Thus the debate had turned full circle. In favour of the concept of pfpopschizophrenia were Kraepelin, Greene and O'Gorman and opposing it, Luther, and Kallman.

Such aetiological preoccupation with the dually diagnosed population is rarely voiced in today's literature. Perhaps this is surprising, as relatively recent evidence suggests that pre-morbid cognitive impairment and social maladjustment may be detected prior to the onset of psychotic symptomatology, in pre-schizophrenic children (Offord and Cross, 1971; Done et al, 1994).

Over the last 25 years, there have been three clinically based studies that have attempted to take a holistic approach to the biological origins of schizophrenia, in subjects with learning disability. The details of these studies are represented in Table 1.

Table one – Biological studies of schizophrenia in people with learning disability from 1972

<u>YEAR</u>	<u>AUTHOR</u>	<u>EPILEPSY</u>	<u>SENSORY IMP.</u>	<u>GENETIC</u>	<u>N</u>
1972	REID	25%	42%	TRI. 21 48XXYY 46XX/47XXX	12
1977	HEATON –WARD	12.5%	18%	45XO/46XX	32
1979	HUCKER ET AL	29%	10%	TRI. 21	14

All three studies used in patient learning disabled populations. The number of subjects recruited varies from 12 to 32. Selection of patients for participation is 'clinically based', with the exception of the study by Hucker et al (1979), no formal operational diagnostic criteria, or control groups were used.

Reid's study of 1972, examined inpatients with co-morbidity in Strathmartin and Liff Hospitals, Dundee. Subjects for the study were referred by colleagues and inclusion was 'based on reaction types described in successive editions of Henderson and Gillespie's Textbook of Psychiatry (1927-1969)'. A clinical interview, physical examination, skull x-ray, karyotype and I.Q. test were routinely performed. Some of the 12 schizophrenic patients also had an electroencephalogram. Although numbers were small, a quarter of patients

had epilepsy and three abnormal karyotypes were noted - one Down's syndrome, one 48XXYY and one 46XX/47XXX.

In the Heaton-Ward study (1977), 32 co-morbid patients were found amongst a total of 1251 patients resident in 4 learning disability hospitals. Patients for inclusion were referred by colleagues from 3 local hospitals and by case note review of the 400 inpatients in the author's own hospital. The diagnostic criteria used were 'my own criteria' and 'the usually accepted clinical criteria'. 12.5% of the study population were epileptic and one patient had a karyotype abnormality - a Turner's syndrome mosaic.

Hucker and colleagues (1979) used Feighner's criteria, 'modified for use in mentally handicapped populations'. Patients were aged 16-65 and all had a WAIS full score of less than 70. They had to have had an episode of psychosis within the last 5 years, in which there was no evidence of dementia or clouding of consciousness, to meet the inclusion criteria. Cases were referred over a one year period and for those cases who had recovered, an interview was held with nursing staff and the case notes reviewed to assess the nature of the illness. A total of 14 schizophrenic patients were assessed, in clinical and physical terms. An EEG, urine screen and karyotype were also performed. The commonest psychopathology was noted to be an incongruity of affect and that patients 'behaved as if hallucinated (with), paranoid delusions (non-affective) and formal thought disorder (were present).' The author's conclude that the

range of psychopathology seen 'reflected the limited personal experiences of the individuals'.

In order to attempt to address the question of the aetiology of co-morbidity, a control group of 40 individuals with learning disability alone were selected. However, it was not possible to match all subjects for I.Q., as many of the controls had not had a standardised I.Q. test, but had been assessed only in terms of adaptive behaviour. No statistically significant differences between the groups, in any of the parameters assessed, were found. Hence the author's concluded, that 'there was no evidence to suggest that associated cerebral damage, perceptual defects or chromosomal abnormalities played any part in the aetiology of the psychoses in the co-morbid group'.

Since 1979, technology has transformed the face of biological psychiatry - M.R.I., functional imaging, brain mapping, linkage analysis, PCR and FISH techniques, have all contributed to a greater understanding of previously enigmatic psychiatric conditions. Few investigators have turned their attention to the co-morbid population. In the absence of evidence to the contrary are we still justified in accepting the conclusions of Hucker and colleagues ?

### 1.3.2 IQ and schizophrenia in the general population

The work of Faris and Dunham (1939), linking schizophrenia with the lower social classes in urban Chicago, resulted in the differentiation of the terms "social drift" and "social underachievement" in the psychiatric literature. They

provided evidence that new cases of schizophrenia in Chicago were concentrated in the run down slum areas of the city, with significantly fewer cases originating from the more affluent peripheral districts. Although this study suggested that the prevalence of schizophrenia was increased amongst individuals in lower socio-economic status groups, it was not possible to comment on the incidence of schizophrenia from this work.

The term social drift was subsequently defined as 'social deterioration occurring after the onset of illness' and the term social underachievement as 'the failure of a sufferer to attain the occupational level of their father' (Jones et al, 1993). Following on from the work of Faris and Dunham, researchers became interested in assessing the pre-morbid levels of functioning of people who subsequently developed psychosis. Their aim was to identify potential behavioural antecedents of the condition.

Early studies in this area concentrated on the retrospective ascertainment of intelligence quotients of pre-schizophrenic children, relative to their peer group, who were presumed to be free of psychiatric illness. Lane, Albee and co-workers at the Western Reserve University, Cleveland provided a series of such studies, in the 1960's, utilising subjects from an urban school system (Lane and Albee, 1963; 1964; 1965; 1968; Albee et al, 1964). In their initial study, intelligence tests from early and late childhood were located for 153 people with adult onset schizophrenia. A third of this sample had attended remedial classes for "dull" children. When compared to a control group of 872

children, who had not developed schizophrenia, a statistically significant drop in IQ scores between early (age 5-8 years) and late (age 11-14 years) childhood were found in the pre-schizophrenic group. However, a subsequent study, by the same authors, later refuted this finding when more suitable control groups were used (siblings and neighbourhood friends) to take into account confounders such as socio-economic status, ethnicity and baseline IQ. When these conditions were controlled for, no childhood IQ decline between pre-schizophrenic children and controls was seen.

The results of subsequent studies, in the urban area, indicated that pre-schizophrenic children performed worse on tests of IQ relative to sibling and neighbourhood controls. This finding was then replicated in pre-schizophrenic children from middle and upper class backgrounds living in suburban areas (Schaffner et al, 1967).

In the last 5 years this finding has again been replicated in two cohort studies where pre-schizophrenic individuals have been shown to exhibit pre-morbid IQ impairment relative to peers (e.g. Jones et al, 1995 (1946 British Birth Cohort); David et al, 1997 (Finnish Army recruits).) The very large numbers of controls in these samples greatly enhances their statistical power.

Following the early studies that focused on one or two consecutive childhood IQ scores, other studies then compared the current morbid IQ of patients with schizophrenia to childhood pre-morbid scores (Albee et al, 1963). Preliminary



results indicated that there were no apparent differences between the two temporally segregated scores. This finding has also been replicated in recent years (Russell et al, 1997).

However, when Albee and colleagues sub-divided their subjects into 'chronic' and 'reactive' subtypes, it was noted that the chronic group had been impaired on their childhood IQ tests relative to controls. This resulted in the theory that people with a reduced pre-morbid IQ may be more susceptible to the development of specific sub-types of the schizophrenia.

In 1971 Offord and Cross studied the school records of 29 pre-schizophrenic children, their siblings and controls, and related to the data obtained to information from contemporaneous hospital records detailing the nature and course of each individual's subsequent illness. The most striking result was that schizophrenic patients with low childhood IQs showed an earlier onset of psychosis and remained institutionalised for significantly longer than schizophrenic patients of average childhood intelligence.

A relationship was therefore established between pre-schizophrenic IQ and disease prognosis. However, it remained unclear as to whether a low childhood IQ was, in itself, predictive of a more malignant form of illness, or inversely, whether an adequate or superior IQ confers a degree of protection against a disease of early onset and chronic course.

It is known that patients with schizophrenia, especially those with severe and persisting illnesses, show evidence of cognitive impairment in adulthood on a variety of neuropsychological tests. (e.g. Klonoff et al, 1970). These observations have led to controversy in the psychiatric literature regarding the nature of the cognitive impairment seen in people with schizophrenia. Some workers regard the cognitive impairment to be progressive and to therefore provide evidence of a degenerative disease process (Bilder et al, 1992), whilst others (Goldberg et al, 1993a; Hyde et al, 1994) regard the cognitive impairment seen to be non-progressive and the result of a static encephalopathy.

There are a variety of studies providing data relevant to each of these two hypotheses. Data supporting the progressive deterioration theory may be obtained from the experimental work of Smith (1964), Ciompi (1980) and Silverberg-Shalev and colleagues (1981). There are also a number of studies suggesting that the most severe deterioration may occur in the first five years after the onset of psychosis (Bleuler, 1972; Abrahamson, 1983; Kolawowski et al, 1985). All these studies have focused on neuropsychological assessments and none have included people with mild learning disability amongst their subjects. Inherent methodological problems also arise when an ageing psychiatric population is studied in this regard, the effects of long term institutionalisation, medication and the high co-morbidity of substance abuse, head trauma and neurological conditions are all potential sources of bias.

The evidence for a static encephalopathy is perhaps more compelling, although based principally on refuting the evidence for a progressive deterioration. Data in support of a static encephalopathy has been collected by retrospective analysis of childhood IQ records (Albee et al, 1963; Russell et al, 1997), serial neuropsychological assessments (e.g. Klonoff et al, 1970; Hoff et al, 1991) and a widening range of other investigative techniques.

Serial neuroimaging studies using both CT scanning (Nasarallah et al, 1986; Illowsky et al, 1988) and MRI (Degreef et al, 1991) show no evidence of structural brain change over time. Post-mortem studies of the brains of people with schizophrenia do not show any evidence of gliosis, which is known to be indicative of active degenerative processes in other cerebral diseases (Roberts et al, 1986; Bruton et al, 1990). Indeed, it has been claimed that the changes in brain cytoarchitecture seen in such studies are themselves evidence for a neurodevelopmental model of schizophrenia and supportive of static encephalopathy theories (Goldberg et al, 1993a). Robust evidence now exists that there is an association between pre-morbid functioning and the longer term clinical course of schizophrenia, including level of social and occupational functioning, treatment response and rate of relapse (e.g. Gittleman-Klein and Klein, 1969; Bromet et al, 1974; Knesevich et al, 1983; Fenton and McGlashan, 1987).

The main methodological problem in this area is that people with pre-morbid learning disability are generally deliberately excluded from study populations. It

is therefore conceivable that the very group of individuals who may develop the most severe form of schizophrenia, in terms of the prognostic features under consideration, have not to date been adequately investigated.

Further research involving people with schizophrenia and an IQ below the normal range may lead to a greater understanding of the generality of schizophrenia.

## CHAPTER TWO

### EPIDEMIOLOGICAL ESTIMATES OF THE CO-OCCURRENCE OF SCHIZOPHRENIA AND LEARNING DISABILITY- A REVIEW

*"The relation between psychoses and subnormal functioning involves two of the most frequent problems in our society. Although there have been a number of studies, we are far from secure in our estimate of the frequency with which this relationship occurs."*

Masland, Sarason and Gladwin (1958)

#### 2.1 Introduction

It has been argued that the relationship between learning disability and psychiatric disorders was first considered by Wells in 1845, when he described cases of mania which he had observed to occur in cretins (Shapiro, 1979). Sir Thomas Clouston (1883) subsequently elaborated on the association in his classic text, *Clinical Lectures on Mental Diseases*. Attempts at categorising and defining psychiatric and emotional disturbances of the learning disabled population, in epidemiological terms, were then initiated (Hurd, 1888). In 1908 Tregold estimated that mental illness occurred 26 times more often in the learning disabled population than the normal population.

Epidemiological studies remain topical today and, despite a wealth of literature, the true details of incidence and prevalence remain elusive. The field is notoriously plagued by methodological difficulties, some of which will be discussed, in the following critical appraisal of available studies. Two main types of study have been undertaken. The first type focuses on in-patient

populations (learning disability or general psychiatric hospitals), the second community based populations.

## 2.2 In-patient based population studies

Table two summarises the results of 13 studies over the course of the last 60 years, which have investigated the prevalence of co-morbidity in learning disability hospital populations. Point prevalence rates for mental illness per se vary in these studies from 15.6% to 58.8%, and for schizophrenia from 0.63% to 18.4%.

Penrose's 1938 survey was the first large scale epidemiological investigation in the area and hence has become a classic. In common with all subsequent studies, until the mid 1980's, no formal diagnostic criteria were used and diagnoses were made idiosyncratically on the basis of clinical experience. Nevertheless, Penrose's figures of 33% for mental illness and 3.7% for schizophrenia remain widely quoted today.

Both James (1939) and Pollock (1944) addressed the issue of mental illness in learning disability within the setting of a special hospital environment (high security / state hospital). The former was based in the United Kingdom at Rampton and the latter in the United States at New York. Both studies found high rates of dementia praecox in the learning disability populations, 8.0% and 18.4% respectively.

Table two - Epidemiology of Co-morbidity- Learning disability hospital in-patient studies.

AUTHORS (YEAR)	TYPE OF FACILITY	TOTAL (N)	NATURE OF L.D.	DIAGNOSTIC CRITERIA USED	PERCENTAGE WITH MENTAL ILLNESS	PERCENTAGE WITH SCHIZOPHRENIA
PENROSE (1938)	L.D. HOSPITAL COLCHESTER	1280	ALL TYPES	NONE	33%	3.7%
JAMES (1939)	RAMPTON STATE HOSPITAL	2382	ALL TYPES	NONE	NOT ASSESSED	8.0% (DEMENTIA PRAECOX)
POLLOCK (1944)	NEW YORK CIVIL STATE HOSPITALS	444	ALL TYPES	NONE	30.6%	18.4% (DEMENTIA PRAECOX)
LECK ET AL (1967)	L.D. HOSPITAL	1652	ALL TYPES	NONE	?	6.2%
PAYNE (1968)	L.D. HOSPITAL	216	ALL TYPES (5-76 YEARS)	NONE	NOT ASSESSED	10% ("PSYCHOTIC")
CRAFT (1971)	L.D. + STATE + PSYCHIATRIC HOSPITALS	568	ALL TYPES (16.5% MILD)	NONE	25% OF MILD (EXCLUDING P.D.)	NOT ASSESSED
WILLIAMS (1971)	L.D. HOSPITALS (ST. BIRINUS GROUP)	752	ALL TYPES	NONE	58.8%	NOT ASSESSED
REID (1972)	L.D. AND PSYCH. HOSPITALS (DUNDEE)	1130	ALL TYPES	REACTION TYPES FROM TEXTBOOK	NOT ASSESSED	3.2%
FORREST & OGUNEREMI (1974)	L.D. HOSPITAL (GOGARBURN, EDINBURGH)	600	ALL TYPES (> 15 YEARS)	DEvised OWN 24 ITEM SCHEDULE	NOT ASSESSED	10% ("PSYCHOTIC OR MENTALLY ILL")
HEATON-WARD (1977)	L.D. HOSPITALS (STOKE PARK GROUP)	1251	ALL TYPES	NONE	NOT ASSESSED	3.4%
WRIGHT (1982)	L.D. HOSPITAL (SURREY)	1507	75% SEVERE, 25% > 60 Y, 50% NO SPEECH	NONE	NOT ASSESSED	1.8% (OF VERBAL PTS)
DAY (1985)	L.D. HOSPITAL (MORPETH)	357	ALL TYPES (> 40 YRS, 35% MILD)	ICD-9	30%	4.5%
CREWS Jr. ET AL (1994)	L.D. HOSPITAL (U.S.A.)	1273	ALL TYPES (10-80 YEARS, 3.5% MILD)	DSM-III-R	15.6%	0.63%

These rates may be construed as a reflection of the hospital admission policy, higher rates of offending, and the perceived dangerousness of co-morbid patients.

The work of Payne (1968) once again uses broad diagnostic categories with no formal criteria, and in common with its contemporaries makes no attempt to sub-define patients in terms of degree of learning disability, age or sex. Hence the studies of Payne, Craft, Williams, Reid, Forrest and Ogunremi, and Heaton-Ward all assume that learning disability is a homogeneous condition. Adherence to this belief implies that individuals with mild disability have the same propensity to develop mental illness as those with severe or profound disability. Today, it is generally accepted that schizophrenia cannot be diagnosed in individuals with I.Q.'s below 50 with any degree of certainty (Reid, 1989a).

Seven of the thirteen studies have populations larger than 1000. However, impressive as these numbers appear, investigators did not always personally examine and assess all patients. Heaton-Ward (1977) "recruited" patients from colleagues and only formally assessed those who he had been told had psychiatric illness. Routine screening of patients not thought to have mental illness was not employed, yet these 'silent' patients were included in the overall population.



The low point prevalence figure for schizophrenia of 1.8%, obtained by Wright (1982), may be explained by a number of factors. Firstly, 75% of the subject population suffered from severe learning disability and 50% of the sample had no speech. The diagnosis of schizophrenia was only made if the patient was able to talk. Secondly, 10% of the study population had Down's Syndrome - it has been suggested that individuals with Down's Syndrome are either less susceptible to the development of schizophrenia, or the condition is generally under-diagnosed (Collacott et al, 1992), relative to other individuals with learning disability.

Formalised diagnostic criteria (ICD-9) were utilised by Day in his 1985 study of middle-aged and elderly people with learning disabilities resident in a long-stay hospital at Morpeth. 35% of the population were mildly learning disabled and all were more than 40 years of age. Despite the passage of nearly 50 years, changing political tides and a prevailing ethos of community care, Day's results are remarkably similar to those obtained by Penrose in 1938.

The final study in table two, Crews Jr. et al (1994), distinguishes itself by reporting a point prevalence of schizophrenia in an in-patient learning disabled population, which is lower than seen in the normal population. This anomaly probably arises as 96.5% of the study population were more than mildly learning disabled (I.Q. <50), and DSM-III-R (American Psychiatric Association, 1987) was used as the project's operational diagnostic criteria. Many of the criteria specified in DSM-III-R, as necessary for a diagnosis of schizophrenia to



be made, are extremely difficult to ascertain in people, such as those assessed in this study, with limited communication skills (Sturmey, 1995).

Despite the many methodological problems which have been encountered in these studies, a pattern seems to be gradually emerging of a point prevalence of schizophrenia amongst mildly learning disabled in-patients of around 3%. In today's health service in the U.K. this figure is certainly an underestimate. The main reason for this being the large numbers of people, with mild learning disability, who are admitted to general psychiatric hospitals and not included in these figures.

Table three describes three North American studies that have investigated the epidemiology of co-morbidity in general psychiatric in-patient units. No data for the U.K. was available at the time of writing. All three studies are retrospective, based on casenote analyses, and utilise formal diagnostic criteria. The majority of subjects in all studies had mild learning disability. In two of the studies a quarter of all learning disability admissions to the general psychiatric units suffered from schizophrenia and in the third study this figure was 17.3%.

These results may be equated with those from table two, i.e. if 30% of an L.D. hospital population has a psychiatric illness, and 3% of the population has schizophrenia, then 10% of the mentally ill population have schizophrenia.

Table three - Epidemiology of Co-morbidity - General psychiatry hospital in-patient studies.

AUTHORS (YEAR)	TYPE OF FACILITY	TOTAL (N)	NATURE OF L.D.	DIAGNOSTIC CRITERIA USED	PERCENTAGE WITH MENTAL ILLNESS	PERCENTAGE WITH SCHIZOPHRENIA
MENOLASCINO ET AL (1986)	GEN. PSYCH. HOSPITAL (U.S.A)	543 (RETROSPEC. OVER 5YRS)	ALL TYPES	?	NOT ASSESSED	25%
ADDINGTON ET AL (1993)	GEN. PSYCH. HOSPITAL (CANADA)	34 (RETROSPEC. OVER 2 YRS)	78% MILD	DSM-IIIR	NOT ASSESSED	25%
PARY (1993)	UNIVERSITY GEN. PSYCH. HOSPITAL (U.S.A.)	247	60% MILD	DSM-IIIR	NOT ASSESSED	17.3%

This contrasts with the figure of around 25% for schizophrenia in the mildly learning disabled mentally ill population of a general psychiatric unit. Although it has been suggested (Pary, 1993a), that this figure may be a little high due to over-diagnosis of schizophrenia by non-learning disability specialists, it seems likely that figures obtained in table two for schizophrenia in learning disability, at least in the mildly learning disabled population, are an underestimate. A significant proportion of individuals with mild learning disability and schizophrenia are admitted to general psychiatric units. In North America this group constitute 25% of all learning disability admissions to general psychiatric units. Perhaps, therefore, a better estimate of the true prevalence of schizophrenia in the mildly learning disabled population is obtained by considering those studies that are community based.

### 2.3 Community based population studies

Table four lists twelve community based studies originating from the United States, Scandinavia and the United Kingdom. In contrast to the hospital based studies, and with the notable exception of the work of Borthwick-Duffy and Eyman (1990), all have index populations of less than 1000. Generally these studies are more concerned with overall prevalence of mental illness in those with learning disability rather than specific conditions. Despite this, six studies give prevalence estimates for either schizophrenia or psychosis.

Table four - Epidemiology of Co-morbidity - Community based studies.

AUTHORS (YEAR)	TYPE OF FACILITY	TOTAL (N)	NATURE OF L.D.	DIAGNOSTIC CRITERIA USED	PERCENTAGE WITH MENTAL ILLNESS	PERCENTAGE WITH SCHIZOPHRENIA
LEMKAU ET AL (1942)	URBAN DISTRICT OF BALTIMORE (U.S.A)	694	ALL TYPES	NONE	NOT ASSESSED	9% "PSYCHOTIC"
BALLINGER & REID (1977)	1. L.D. HOSPITAL 2. ADULT CENTRE	75	OLDER, SEVERE YOUNGER, MILD	STANDARDISED CLINICAL INTERVIEW SCHEDULE (SCIS)	31% 13%	NOT ASSESSED
CORBETT (1979)	CAMBERWELL (COMMUNITY & HOSPITALS)	402	ALL TYPES ADULTS 13.7% MILD	ICD-8	46%	3%
JAKAB (1982)	CLINIC FOR L.D. CHILDREN (U.S.A)	595	ALL TYPES CHILDREN	NONE	30%	9%
EATON & MENOLASCINO (1982)	SCHOOLS, SOCIAL SERVICES, PHYSICIANS. (U.S.A.)	798	ALL TYPES 43% 11-20 YRS 51% ADULTS	DSM-III	14.3%	3%
LUND (1985)	SCANDINAVIAN - "EPIDEMIOLOGICAL CRITERIA"	302	ALL TYPES ALL ADULT	COMPUTERISED DIAGNOSIS - DSMIII + MOD. FEIGHNER	27.1%	1.3% (ALL I.Q. >50) (5% PSYCHOSIS OF UNCERTAIN TYPE)
GILLBERG ET AL (1986)	SAMPLE OF L.D. CHILDREN BORN 1966-70 (GOTEBORG)	149	CHILDREN AGE 13-17 56% MILD, 44% SEVERE	DSM-III + SPITZER	57%	1%
IVERSON & FOX (1989)	RANDOM L.D. POPULATION SAMPLE (U.S.A.)	165	ALL TYPES ALL ADULTS	USED PIMRA (BASED ON DSM-III)	35.9%	NOT ASSESSED
BORTHWICK-DUFFY & EYMAN (1990)	CALIFORNIA DEVELOPMENTAL SERVICES (CLIENTS) DAY PROGRAM FOR L.D. IN CHICAGO (U.S.A)	78,603	ALL TYPES, AGES 0-86, 28.9% MILD.	DSM-III-R	MILD = 54.3% MODERATE = 25.7% SEV.+PROF. 20.0%	NOT ASSESSED
REISS (1990)		205	ALL TYPES 45.8% MILD	REISS SCREEN (BASED ON DSM-III-R)	39%	NOT ASSESSED

Several familiar methodological problems, already identified in the in-patient based studies, are once again present. Specifically, the lack of formalised diagnostic criteria in two studies (Lemkau et al, 1942; Jakab, 1982), the variable stratification of severity of learning disability and age within the study populations, and the sampling strategies employed. This latter point is perhaps rather more poignant in these studies than the in-patient studies. Sampling techniques include usage of Scandinavian National registers (Larsson & Sjorgen, 1954; Hallgren & Sjorgen, 1959; Lund, 1985; Gillberg et al, 1986), usage of locally established registers (Corbett, 1979), random population samples of people with learning disability (Lemkau et al, 1942; Iverson & Fox, 1989), dependence on referral from a variety of agencies (Eaton & Menolascino, 1982) and surveys of service users (Ballinger & Reid, 1977; Jakab, 1982; Borthwick-Duffy & Eyman, 1990; Reiss, 1990).

One study attempts a direct comparison between an in-patient sample and community based sample (Ballinger & Reid, 1977). As would be expected a higher rate of mental illness is found in the in-patient sample relative to the community sample. However, numbers are comparatively small and subjects from the two groups were not matched for age or degree of learning disability. Consequently, the in-patient sample comprises an older and more severely handicapped group of individuals than the community sample.

Two studies focus on children and adolescents (Jakab, 1982; Gillberg et al 1986). The former uses no formalised diagnostic criteria and has a relatively

high estimate of the prevalence of schizophrenia (9%) compared to the total prevalence of mental illness seen (30%). The latter employs a combination of the DSM-III and Spitzer Criteria, and has a relatively low prevalence of schizophrenia (1%) relative to the total prevalence of mental illness seen (57%).

'Epidemiological methods' were used to obtain a population sample in the study by Lund (1985) and a computerised diagnosis utilising DSM-III and modified Feighner criteria obtained. Surprisingly the rate of schizophrenia (in people with an I.Q. over 50) was comparatively low (1.3%). This is perhaps accounted for by the diagnosis of psychosis of 'uncertain type' made in 5% of subjects.

Borthwick-Duffy and Eyman (1990) surveyed 78,603 individuals known to the California Developmental Services. Inclusion in a centralised database of clients necessitated a diagnosis based on DSM-III-R Criteria to be made by the registering clinician, if referral to the mental illness services was made. However, not all individuals were screened by a physician, and so the possibility that some individuals had undetected mental illness remains. Notwithstanding this, the sample size is large, and perhaps the most valuable finding is the association between the level of disability and prevalence of mental illness. Those with the mildest forms of learning disability have a higher detected rate of mental illness (54.3%) relative to individuals with more severe learning disability.

## 2.4 The true prevalence of mental illness in learning disability

As has been demonstrated, a consensus on the true prevalence of mental illness in learning disability, has not yet been ascertained and perhaps will never be available, due to inherent methodological problems.

Studies performed in the U.S.A. in the early 1980's indicate that individuals with learning disabilities are more prone to a 'diagnostic overshadowing phenomenon' (Reiss et al, 1982; Alford and Locke, 1984), than other dual diagnosis groups. Hence, the presence of learning disability in an individual serves to reduce the diagnostic significance of symptomatology usually taken to be indicative of psychosis, and generally not considered to relate to intellectual impairment per se.

Using clinical psychologists as assessors, such diagnostic overshadowing was observed to be independent of the assessor's degree of professional experience with the learning disabled population (Reiss and Szyszko, 1983). There is a sparse literature on the ability of medics to overcome the pitfalls of diagnostic overshadowing in dual diagnoses patients. In the case of individuals with concurrent mild learning disability and schizophrenia this is an area of interest.

It has also been suggested that factors such as 'psychosocial masking, baseline exaggeration, intellectual distortion and cognitive disintegration'



(Sovner, 1986) may be contributing to the underestimation of the true prevalence of mental illness in the learning disabled population.

However, it has been consistently demonstrated that people with mild learning disability have higher rates of mental illness than those seen in the normal population. Additionally, the point prevalence of schizophrenia in the mildly learning disabled appears to be in the order of three times (approximately 3%) that seen in the normal population (1%). In the light of methodological criticism, it would appear that such figures are an under, rather than an over estimate of the true prevalence.

## CHAPTER THREE

### WHY ARE PEOPLE WITH MILD LEARNING DISABILITY MORE PRONE TO DEVELOP SCHIZOPHRENIA ? - FIVE HYPOTHESES

*'It is important never to lose sight of the fact that all diseases and diagnostic categories are simply concepts'*

R.E. Kendell 1987

#### 3.1 Introduction

Given that the body of evidence suggests that individuals with mild learning disability have a higher point prevalence of schizophrenia than the general population, speculation may now begin as to why this should be so. In this chapter five tentative hypotheses will be critically explored. It is not suggested that any one hypothesis is definitive, this would appear to be rather naive. It is more likely that several mechanisms are operating in varying degrees to produce an overall effect.

The hypotheses to be considered are;

1. A chance co-occurrence ?
2. A common aetiology ?
3. An epiphenomenon ?
4. A 'severe' schizophrenia ?
5. A *de novo* condition ?

### 3.2 A chance co-occurrence ?

In the past some researchers have held the belief that no aetiological relationship, of either a psycho-social or organic nature, exists between learning disability and schizophrenia.

In 1925 Bartemeier refuted any suggestion of a direct aetiological relationship between dementia praecox and mental deficiency. However, he conceded that he believed it possible for the two syndromes to originate independently and for each to subsequently influence the other's course. No experimental evidence was offered to substantiate his claim.

The concept was elaborated upon (Brugger, 1928) by using family studies. He conducted extensive 'kinship studies' on a heterogeneous collection of people with feeble-mindedness. Brugger found no increase in schizophrenia, or other psychoses, in the relatives of feeble-minded subjects compared to the normal population. He claimed that this finding alone was sufficient to conclude that when schizophrenia and feeble-mindedness co-occur in the same individual, they do so only by chance (Kallman et al, 1940-41).

Following in depth study of the case histories of monozygotic and dizygotic twins, showing various combinations of concordance and discordance for both schizophrenia and learning disability, Kallman et al (1940-41) agreed with Brugger's conclusions.

However, by focusing their attention on genetic aetiological components, the last two investigators neglected a fundamental epidemiological point which negates their hypothesis. It has already been shown that the point prevalence of schizophrenia is increased in mild learning disability. If the two conditions occurred together by pure chance then the likelihood of co-occurrence would be considerably less than the point prevalence of each in the normal population. For example, if the point prevalence of schizophrenia (in the normal population) is taken as 1% and the point prevalence of mild learning disability (of all aetiologies) is taken as 3%, then the likelihood of the two conditions occurring together by chance alone is at least  $((1/100) \times (3/100))$  0.0003 in the normal population.

### 3.3 A common aetiology ?

Considering 250 consecutive admissions to a psychiatric hospital, Johnson (1968) showed that 12% of these admissions had concurrent physical illness, which was perceived to be an important aetiological factor in the presenting mental disorder. More specifically, considering schizophrenia, Johnstone and colleagues (1987) found that 6% of first episode schizophrenic cases used in a neuroimaging study (who had already been screened by physicians to exclude organicity) had evidence of organic disease.

It has long been appreciated that neurological disorders may mimic the presentation of a functional psychosis. However, what remains unclear is the

extent to which schizophrenia may itself be associated with unequivocal brain pathology, of presumed aetiological significance. Although macroscopic pathology may be detected today by sophisticated neuroimaging techniques a substantial amount of microscopic pathology is potentially overlooked. The recent introduction of functional neuroimaging techniques (SPECT, PET, fMRI) have introduced a new dimension to the equation. Through the application of these techniques, the biological basis of thoughts, cognition and behaviour have become potentially definable in terms of brain metabolism. Consequently the philosophic conundrum termed the "mind / body problem" has become arguably obsolete. The workings of the mind may now be equated with workings of the body.

Feinstein and Ron (1990) investigated 65 psychotic patients attending The National Hospital for Nervous Diseases, with respect to phenomenology and outcome. All subjects had previously been shown to have unequivocal evidence of brain pathology and 53 were diagnosed as having schizophrenia according to the CATEGO system based on The Present State Examination Interview (Wing et al, 1974). Although the formal medical diagnoses varied considerably (including epilepsy, trauma, space occupying lesion, multiple sclerosis and movement disorders) in these cases, no relationship could be found between the site or nature of brain pathology and type of psychoses seen. However, schizophrenia was shown to be commoner in patients with brain pathology than other forms of psychosis. The commonest medical

diagnosis in this study was epilepsy (16 idiopathic cases and 21 secondary). 30 of the 37 epileptic cases were diagnosed as having schizophrenia.

Epilepsy is seen more frequently in people with learning disability than the normal population. Although epilepsy per se is a symptom and not a discrete pathological entity, few dispute that it signifies the presence of organicity.

The relationship between epilepsy and schizophrenia is complex. Nevertheless, the increased incidence of epilepsy in people with mild learning disability and people with schizophrenia provides a common factor of perceived aetiological significance. Several questions therefore present themselves. Firstly, what proportion of people with a dual diagnosis of schizophrenia and mild learning disability have epilepsy ? Secondly, is any one form of epilepsy commoner in these individuals ? Finally, would treatment of the epileptic condition per se (be it idiopathic or secondary in origin) alleviate or palliate the symptoms of schizophrenia ?

It is becoming increasingly clear that organic causes of psychosis may also be determined in people with learning disability. The work of Crome and Stern (1972) has shown that 90% of those with moderate or more severe intellectual disability have demonstrable brain pathology at autopsy.

Biochemical anomalies may produce both psychoses and learning disability conditions in the same individual e.g. Wilson's disease, phenylketonuria,

Hartnup disease and porphyria. Similarly, a number of drugs and poisonous substances have been shown to produce learning disability with superimposed mental illness e.g. mercury (Pink disease, Hunter and Russel syndrome, Minamata disease), lead (plumbism) (Jancar, 1979).

Recent advances in cytogenetics have helped to elucidate groups of individuals with abnormal chromosomal constitutions and resultant learning disability, who have a specific propensity to develop psychoses. e.g. Intrachromosomal insertion of chromosome 13 (Roberts et al, 1986), Klinefelter's Syndrome (Wakeling, 1972; Roy, 1981), Velo-Cardio-Facial Syndrome (Shprintzen et al, 1992; Pulver et al, 1994a; Lindsay et al, 1995).

It is therefore possible that the excess of schizophrenia seen in the mildly learning disabled population may be resultant upon the two conditions having a common organic aetiology. Popular avenues of research, independently seeking to clarify aetiology in both conditions, include; the roles of perinatal insult, childhood illnesses / infection, and genetic influences (with particular reference to the importance of trinucleotide repeats in Fragile X syndromes, schizophrenia (O'Donovan et al, 1995) and people with schizophrenia and Fragile X (Jönsson et al, 1995). Perhaps a cognisance amongst researchers of the relatively neglected co-morbid population may result in a greater generalised understanding of the aetiologies and complex relationships between schizophrenia, learning disability and the co-morbid condition.

### 3.4 An epiphenomenon ?

The essential features of learning disability are; significantly sub-average general intellectual functioning, resulting in or associated with, deficits or impairments in adaptive behaviour, with onset before the age of 18 (APA, 1987). With the exception of the age of onset criteria, this definition is broad, non-specific and hence constitutes a heterogeneous array of individuals, some of whom have complex special needs. Even when comprehensive assessments are performed the cause of learning disability remains elusive in 30% of cases (Einfield, 1992).

People with learning disability have deficits or impairments, of varying degrees, in a range of adaptive functioning. These may be categorised into 5 main areas; social, cognitive, sensory, motor and behavioural. Impaired functioning in any one area may lead to impairment in any other e.g. blindness leads to motor and social problems, interpersonal skills deficits may lead to behavioural problems. The constellation of impairments manifested by any individual is therefore complex, interrelated and interdependent.

Schizophrenia is also a heterogeneous condition. Although more narrowly defined in the psychiatric literature than learning disability per se, it remains a multi-faceted syndrome, with a diverse range of presentations. However, schizophrenia may also result in impairments, of varying degrees, in a range of



adaptive functioning. These include the same five main areas; social, cognitive, sensory, motor and behavioural, mentioned above.

There are areas of overlap between the adaptive deficits seen in both conditions.

i.e.

1) Behaviours such as self mutilation, aggression and emotional volatility may occur in both conditions.

2) There is an increased frequency of abnormal involuntary and voluntary movements (not thought to be the result of medication) in people with learning disability (Rogers et al, 1991), people with schizophrenia (Owens et al, 1982) and children destined to develop schizophrenia (Walker et al, 1994) relative to the normal population.

Given that there are areas of overlap of adaptive impairment in people with schizophrenia and people with learning disability, it is not perhaps not too extreme to consider that a complex interrelationship may exist between the two conditions. Hence a deficit in one area in an individual with learning disability may render them susceptible to develop impairment associated with schizophrenia, in either that area of adaptive functioning, or another related area.

i.e.

1) It has been well documented that people with deafness (commonly seen in learning disability) are more susceptible to develop paranoid psychoses, which are characterised by auditory hallucinations and persecutory delusions (Cooper et al, 1974; British Medical Journal, 1977).

2) Some children who later go on to develop schizophrenia show evidence of social competence deficits in childhood (Baum and Walker, 1995) which often persist throughout the course of the adult illness. Hence, it may be stated, that people with social deficits evident from an early age are susceptible to the development of schizophrenia in later life.

Viewed in these terms the occurrence of schizophrenic symptoms in individuals with learning disability may, in some instances, be regarded as an epiphenomenon. The mechanism of such an epiphenomenon may be hypothesised by considering cognitive abnormalities as a basis for the evolution of schizophrenic symptoms. A review of work in this area, focusing on the selectivity of information processing, is provided by Hemsley (1994). Selective attention mechanisms and filter theories are critical to an understanding of this area, yet as Hemsley indicates such terms are often vaguely defined.

A clearer model may be derived from Strauss (1987). He argues that particular aspects of a schizophrenic patient's functioning relate to control mechanisms that "involve conscious and unconscious psychological processes that focus on

regulating the amount of demand faced to fit the adaptive capacity available". The corollary of this assumption is that if one's adaptive capacity is compromised (as may be the case in some individuals with learning disability), then such processes may readily become 'overloaded' and themselves become prone to malfunction. In some circumstances, this may result in the evolution of symptoms usually associated with a schizophrenic illness. Overload of these processing mechanisms as they pertain to schizophrenia is exemplified by a case history of a schizophrenic patient, reported by Matussek (1952), the patient states " I may look at my garden, but I don't see it as I normally do. I can only concentrate on details. For instance I can lose myself in looking at a bud on a branch, but then I don't see anything else" (cited by Hemsley, 1987).

Utilising the premise that faulty cognitive processing mechanisms may underlie schizophrenic symptoms it is possible to conceptualise schizophrenia in people with mild learning disability as an epiphenomenon, consequent upon cognitive impairment.

### 3.5 A severe schizophrenia ?

Pre-schizophrenic children have a lower IQ than children who do not develop schizophrenia (Russell et al, 1997) and adult schizophrenic patients show evidence of cognitive impairment in some areas (Klonoff et al, 1970). Such

impairment appears to be specific to schizophrenia amongst the psychoses (Albee and Lane, 1963; Jones et al, 1993).

It is unclear whether the cognitive impairment associated with schizophrenia is static or progressive in nature, but perhaps the former theory is more persuasive at the present time (chapter one). The degree of cognitive impairment present, both in childhood and at first onset of illness, is predictive of the subsequent course of the disease. Those patients with more marked cognitive impairment generally have a poorer prognosis (Gittleman-Klein and Klein, 1969; Bromet et al, 1974; Knesevich et al, 1983; Fenton and McGlashan, 1987) in many spheres of functioning.

Given these facts it seems that people with pre-morbid cognitive impairment, within the mildly learning disabled range, are not only at risk of developing schizophrenia, but schizophrenia of a particularly severe form with a particularly poor prognosis.

It is conceivable that such individuals in fact suffer from an extreme form of schizophrenia, which presents at an early age with cognitive impairment, prior to the onset of the classical features of psychosis. A diagnosis of mild learning disability is made in childhood and this diagnosis persists, beyond the diagnosis of schizophrenia, into later years. If this is the case, we are yet to learn what the true characteristics of severe schizophrenia are.

Given that the majority of epidemiological prevalence studies of schizophrenia also exclude people with learning disability, we may not be aware of the true incidence of the disease or its distribution amongst the social strata. It is therefore possible that schizophrenia may be commoner amongst people from lower socio-economic backgrounds, as a higher incidence of learning disability occurs in this setting.

### 3.6 A *de novo* condition ?

The characteristics and course of schizophrenia, as it occurs in people with mild learning disability, has not been clearly defined. Few researchers today contest the view that schizophrenia is an aetiologically heterogeneous syndrome.

None of the latter three hypotheses above preclude the possibility that schizophrenia, as it occurs in people with pre-morbid cognitive impairment, may be a *de novo* condition. Attempts to characterise the nature of this condition have historically been frustrated by ethical and methodological difficulties. With new technology at our disposal and the greater diagnostic clarity offered by modern classification systems, it may be possible, through systematic inquiry, to determine via controlled study the extent to which this form of psychosis is comparable to schizophrenia in the general population.

## PART TWO

### CHAPTER FOUR

#### INVESTIGATING THE BIOLOGICAL AND PSYCHOLOGICAL MARKERS OF PSYCHOSIS IN PEOPLE WITH MILD LEARNING DISABILITY

*'The clinical and research hole into which these patients have fallen is reminiscent of the eugenics period'.*

T. Turner (1989)

#### 4.1 Aims of this investigation

1. To investigate and characterise the nature of schizophrenia in people with mild learning disability.
2. by evaluation of clinical aspects of the condition, neuropsychological variables, neurological findings, measurement of adaptive behaviour, family history information and karyotypic analysis, relative to two age and sex matched control groups (one group of people with mild learning disability and the other group of people with schizophrenia).
3. To utilise these data to explore possible reasons for the reported increase in point prevalence of schizophrenia in people with mild learning disability, relative to the normal population.
4. To seek clues as to the aetiology of the generality of schizophrenia by the study of this unusual co-morbid population.

## 4.2 Selection and recruitment of co-morbid subjects

One of the main problems encountered by researchers in this area is subject recruitment. A recent study (Meadows et al, 1991) drew upon learning disability services 'from several south London health districts' to recruit a relatively small number of people (N = 25 ), with a diagnosis of both mild learning disability and schizophrenia. This recruitment problem is compounded by the fact that in many areas, such patients may not be exclusively cared for by any one psychiatric speciality. Dependent upon local operational policies, co-morbid patients may be found on the caseloads of general adult, learning disability, or forensic psychiatrists. A degree of 'clinical flux' may also exist between sub-specialities. Therefore, from a practical point of view, an individual patient may be involved with several services throughout their psychiatric career. This further serves to complicate subject selection for large scale studies, if ascertainment bias is to be avoided.

Since 1970, the Information and Statistics Division (ISD) of the Scottish Health Department has collated and stored data on all episodes of psychiatric in-patient admissions in Scotland. The data is received centrally by ISD, following the completion of a standardised form (Standardised Mortality Return 4; SMR4) at the base hospital. Information from the SMR4 is entered into a computer database, and this facilitates record linkage with concurrently held health and census data (Kendrick and Clark, 1993). This database has made it possible to identify people with the concurrent discharge diagnoses of mild learning

disability and schizophrenia, as made by their responsible medical officers, throughout Scotland. It is assumed that there are relatively few people with such diagnoses who have not had at least one episode of inpatient psychiatric hospital care. Furthermore, the SMR4 form is completed by psychiatrists working in all psychiatric sub-specialities in Scotland and so potential ascertainment bias is reduced.

With the assistance of ISD, it was ascertained that 40-50 new cases of schizophrenia or paranoid states (ICD 9 diagnoses) arise in the learning disabled population in Scotland each year and require hospital admission. Preliminary enquiries in 1992, when this study was first conceived, indicated that there were potentially 248 people with co-morbid discharge diagnoses of mild learning disability and schizophrenia, or paranoid states, aged between 16 and 65, in the Fife (N=87) and Lothian (N=161) areas. Only ten of these people were then believed to be currently resident in a psychiatric hospital.

The population in Fife and Lothian is relatively stable and although some people will naturally move out of the area, migration is generally less commonplace than in comparable urban areas in England. This is believed to be particularly true for people with learning disability who rarely seek open employment and are less likely to marry than their contemporaries in the normal population.



An application was made to the Privacy Advisory Committee of ISD to obtain the names of these co-morbid individuals, names of psychiatric hospitals they had been admitted into, the dates of the first and last admissions, and case record numbers. Release of this data was authorised to the investigator by ISD and permission obtained from the Fife and Lothian Regional Ethical Committees for the study to proceed. Individual hospitals and consultants gave permission for the investigator to access named case notes.

RDC (Spitzer et al, 1975), DSMIII-R (American Psychiatric Association, 1987) and St. Louis Criteria (Feighner et al, 1972) for schizophrenia were applied to the casenotes. Attendance at remedial education was taken as indicative of pre-morbid cognitive impairment and was pre-requisite to inclusion in the study cohort. In many cases the subject had attended schools in the local area and this made it possible to locate community health records, compiled during childhood, which often contained serial educational psychology assessments and an estimates of IQ. Only those people with a pre-morbid IQ believed to be in the mild learning disability range i.e. 50-70 were included in the study cohort.

Individuals known to have Down's syndrome were excluded from the cohort as cognitive testing was to form an integral component of the study protocol and these people have an increased risk of developing Alzheimer's disease (Heston, 1982).

Once a suitable subject had been identified from case notes, letters requesting permission to approach the subject, to invite them to participate in the study, were sent to the consultant psychiatrist responsible for their care (if applicable) and their GP. Discussion with the GP (all of whom were telephoned) and psychiatrist established the most appropriate way to make contact with the individual, via a third party who knew them well. The practical arrangements for meeting individual subjects varied greatly.

Permission was obtained from the social work department to interview identified subjects in adult training centres and in these circumstances introductions were arranged by key workers, who had previously asked the subject if they would see a researcher. In other cases; community nursing staff, social workers, ward based nursing staff, day hospital staff, general practitioners, psychiatrists, support workers or carers facilitated introductions.

The co-morbid group were the most difficult group to successfully engage in the study, just over half of those people approached participated (N=39; i.e 54.2% of those approached). The reasons for non-participation are shown in table 5.

#### 4.3 Selection and recruitment of control subjects

##### 1) Control subjects with schizophrenia

These subjects were selected by reference to the Lothian Psychiatric Case Register and had all had at least one episode of in-patient care where the recorded primary discharge diagnosis was schizophrenia (ICD-9). Control schizophrenia subjects were matched to index co-morbid subjects for age (within 5 years) and sex. RDC (Spitzer et al, 1976), DSMIII-R (APA, 1987) and St. Louis Criteria (Feighner et al, 1972) for schizophrenia were applied to the casenotes. Individuals conforming to DSMIII-R Criteria for schizophrenia and with no documented evidence of pre-morbid cognitive impairment or remedial education were selected.

As with the co-morbid index group, permission was sought from both psychiatrists and general practitioners prior to approaching the subject and advice sought on the most appropriate way to make contact. A total of 53 potential subjects were approached and 34 participated (64.2%), the reasons for non-participation are shown in table 5.

#### ii) Control subjects with mild learning disability

These subjects were selected by reference to the Lothian Psychiatric Case Register and active case lists of the community learning disability nursing service. Control learning disability subjects were matched to index co-morbid subjects for age (within 5 years) and sex. Case records were located and individuals with a documented IQ between 50 and 70 selected. Individuals with Down's syndrome, a history of psychosis or current neuroleptic usage were excluded.

Permission was sought from both psychiatrists and general practitioners prior to approaching the subject and advice sought on the most appropriate way to make contact. A total of 30 potential subjects were approached and 28 participated (93.3%), the reasons for non-participation are shown in table five.

Table Five – Outcome of approach to subjects to participate

<u>OUTCOME OF APPROACH</u>	CO-MORBID (N=72)	SCHIZOPHRENIA (N=53)	LEARNING DISABILITY (N=30)
LOST	7	4	1
SUBJECT SEEN BUT REFUSED	6	4	1
CONSULTANT REFUSED	6	1	0
SUBJECT NOT SEEN BUT REFUSED	3	6	0
SUBJECT WITHDRAWN (ILL)	6	1	0
GP REFUSED	2	2	0
ABANDONED	0	1	0
IN SPECIAL HOSPITAL	1	0	0
DIED DURING STUDY	1	0	0
SUBJECT'S CARER REFUSED	1	0	0
TOTAL ATTRITION	33 (45.8%)	19 (35.8%)	2 (6.6%)
TOTAL COMPLETED	39 (54.2%)	34 (64.2%)	28 (93.3%)

4.4 The study protocol

Subjects were visited at a place of their choice e.g. home, adult training centre, GP surgery, psychiatric out-patient clinic, day hospital, ward. In the case of co-morbid subjects introductions were made by a third party, as described above.

At the time of the first meeting a full description of the protocol was given to subjects. If they then wished to take part arrangements were made to meet on a second occasion to answer any questions prior to taking consent to participate. A subject information sheet was left with the subject in the

intervening time. This described the protocol and gave the name and contact details of the investigator in addition to the name and contact details of an independent doctor, who knew of the study but was not directly involved and would be able to discuss the study with the subject should they wish to do so.

Case records were reviewed to provide sociodemographic and clinical information for each subject. The diagnostic validity of the Schizophrenia and Affective Disorders Schedule - Lifetime version (SADS-L; Endicott and Spitzer, 1978) for schizophrenia in people with mild learning disability has been shown to be acceptable for research purposes (Meadows et al, 1991). The SADS-L and Positive and Negative Syndrome Scale (PANSS; Kay et al, 1987) were administered to all subjects.

All subjects were asked to complete the Quick IQ Test (Ammons and Ammons, 1962). The Quick IQ Test does not give such a robust measure of present IQ as a standard test like the Weschler Adult Intelligence Scale. However, it is more suited for use with the subjects in this study as it is quicker to administer. In a study of schizophrenia (Frith et al., 1991), the WAIS and the Quick test were both applied to a subset of the subjects and gave very comparable results (WAIS 83.6, Quick Test 78.7, correlation between WAIS and Quick Test scores 0.91). A National Adult Reading Test (NART; Nelson and O'Connell, 1978) was given to control subjects with no known history of learning disability, to confirm a pre-morbid IQ within the normal range. The Rivermead Behavioural Memory Test (Wilson et al, 1985) was also given to all subjects.

Each subject was neurologically assessed using the Neurological Evaluation Scale (NES; Buchanan and Heinrichs, 1989). Ratings of movement disorders were completed using the Abnormal Involuntary Movement Scale (AIMS; Guy, 1976), Targetting Abnormal Kinetic Effects Scale (TAKE; Wojcik et al, 1980) and Dyskinetic Identification System; Condenser User Scale (DISCUS; Sprague et al, 1989). An assessment of minor physical anomalies was made using the Waldrop Scale (Waldrop et al, 1968).

The adaptive behaviour of each individual was assessed using the Vineland Adaptive Behaviour Scale (VABS; Sparrow et al, 1984a), which was administered to a carer or relative, with the permission of the subject.

A family history of learning disability or psychosis was sought by meeting with a relative (where possible), questioning the subject and reviewing case records. All index subjects with mild learning disability and schizophrenia were asked to provide a blood sample for karyotypic analysis.

The time taken for individuals to complete the protocol varied greatly. Subjects with co-morbidity were visited between 5 and 17 times, the average being 6-8 times; on some occasions the subject did not want to take part on that day or forgot about the appointment. People with schizophrenia alone generally completed the protocol in 4-5 visits and people with learning disability alone in 5-6 visits.

#### 4.5 Time scale of the study

The study was first planned in early 1993. The author was awarded a three year Wellcome Research Training Fellowship in Mental Health to conduct the work, beginning March 1994. The first six months were spent locating casenotes and identifying potential co-morbid subjects, raising awareness of the study amongst colleagues in both general psychiatry and learning disability services, and obtaining permission to see subjects in social services facilities, day hospitals and voluntary sector premises. The author met with all community psychiatric nurses in Lothian to speak about the project and met with social work team managers to obtain permission for social work staff to introduce the investigator to subjects in Fife and Lothian.

By Autumn 1994 subjects were participating in the study and data collection continued until the end of the project in February 1997. All data obtained were entered into an excel spreadsheet at the time of collection. A part-time research assistant was employed for 18 months from March 1995 to accompany the author on visits to subjects in the community and assist with paperwork.

In February 1996, a Wellcome Fellow was appointed for 30 months to recontact those subjects who had participated in the study and invite them to have a magnetic resonance imaging scan of the head performed. The Wellcome appointee (Dr T. Sanderson) accompanied the investigator on visits

to new subjects and conducted some of the investigations under the supervision of the author.

The core project ended in February 1997. Since this time statistical analysis of the results has been conducted using SPSS and the findings have been evaluated.



## CHAPTER FIVE

### A SOCIODEMOGRAPHIC DESCRIPTION OF THE STUDY POPULATION.

*"The age of the patients has a decided influence of the course of the disease..... Men have a somewhat larger share in the unfavourable form of silly dementia; women on the other hand have a greater tendency to paranoid forms."*

Kraepelin, 1919

#### 5.1. Introduction

The data presented in this chapter was derived from a variety of sources - self report, informant report (relative and carer) and case records. Siegelman and colleagues (1982) have emphasised the importance of checking the responses of a learning disability population to open-ended questions with an informant's account to improve reliability. This was done where possible with all data obtained directly from interviews with subjects.

#### 5.2. Method

Subjects were interviewed in a place of their own choosing. This obviously varied from one individual to another, people were seen in their own home, a relative's home, their place of employment, adult training centres, a church drop in centre, social work facilities, hospital out patient departments, psychiatric day hospitals, and hospital wards. When interviewing people with mild learning disability for this study the use of yes / no questions was avoided in an attempt to minimise potential acquiescence bias i.e. the subject responding affirmatively regardless of the content of the question. All interviews

were conducted at the subject's own pace without constraint of time. It was not unusual to terminate an interview at the request of the subject, or suggestion of the interviewer, with plans to return and complete in the near future, often the next day.

The General History Questionnaire (appendix one) was completed for all subjects from information derived from an extensive review of available case notes, an interview with the subject in all cases, and usually an interview with both a carer and relative, with the consent of the subject. The General History Questionnaire was designed specifically for this study by the author to incorporate *a priori* items of interest e.g. service utilisation, epilepsy, previous IQ assessments. The basic framework of the questionnaire was derived from the Schizophrenia Survey Form (Johnstone et al, 1981).

The General History Questionnaire was completed for all 101 subjects. The coded data from the General History Questionnaire was then entered into an excel database and finally into SPSS. Statistical analysis was conducted using one-way ANOVA with post-hoc least significant difference test, Student's Independent t-test, Chi-Squared test, and the Mann-Whitney U Test.

### 5.3.Sociodemographic results

#### 5.3.1. Age, gender and IQ.

The total sample comprised 39 subjects with the co-morbid state (mild learning disability and schizophrenia), 34 controls with schizophrenia and 28 controls with mild learning disability. The mean age of the subjects with co-morbidity was not significantly different to either the schizophrenia or mild learning disability control groups (48.6, 48.6, 47.2, years; respectively). There were no significant gender differences between groups, female subjects constituted between 43% and 46% of all three groups.

The mean Quick IQ score of co-morbid subjects was not significantly different to that of learning disability control subjects (60.5 and 64.3, respectively; t-test  $p=0.560$ ). In the schizophrenia control group the NART scores (range 85-128) suggested that no subject had a pre-morbid IQ within the mild learning disability range (50-70).

### 5.3.2. Social class and marital status

An attempt was made to describe the social class of each subject by reference to the occupation of their father and categorisation was determined by reference to the occupational tables of the Registrar General (HMSO, 1980). Group III was not split into manual and non-manual occupations. The results of social class determinations are shown in table six with marital status and living circumstance data. It was not possible to ascertain the nature of paternal occupation in only 8.8% of control subjects with schizophrenia. In contrast, paternal occupation could not be determined in approximately one third of co-morbid and learning disability control subjects. This was mostly due to the

subject being adopted, having no knowledge of their father, or not being able to recall the nature of their father's occupation.

Where paternal occupation was known, most subjects with co-morbidity and learning disability were from classes III, IV and V and patients with schizophrenia were from classes II III and I. These results are statistically significant ( $\chi^2 = 27.7$ , d.f. =10,  $p=0.002$ ). The majority of all subjects are single. There are no significant differences between groups in terms of marital status.

### 5.3.3 Living circumstances

The majority of subjects in all three groups were not living in hospital accommodation. There were no statistically significant differences between co-morbid subjects and schizophrenia controls in terms of hospital in-patient status at the time of the study. It is of interest to consider the living circumstances of the co-morbid group in more detail, as other studies of this population have tended to focus specifically on hospital in-patients (Reid, 1972; Heaton-Ward, 1977; Hucker et al, 1979).

44.1% of subjects with schizophrenia lived alone, contrasting with only 12.8% of co-morbid subjects and 17.9% of learning disability subjects. 48.8% of co-morbid subjects, 28.6% of learning disability subjects and 8.8% of subjects with schizophrenia were living in non-hospital supported accommodation. This accommodation was generally operated by either social services or charitable organisations. The level of support provided was variable - some placements

Table six - Social class, marital status and living circumstances

VARIABLE	CO-MORBID GROUP (N=39)		SCHIZOPHRENIA (N=34)		LEARNING DISABILITY (N=28)	
	NUMBER	PERCENTAGE	NUMBER	PERCENTAGE	NUMBER	PERCENTAGE
SOCIAL CLASS						
UNDETERMINED	13	33.3	3	8.8	10	35.7
I	1	2.6	4	11.8	1	3.6
II	3	7.7	9	26.5	1	3.6
III	15	38.5	15	44.1	5	17.9
IV	5	12.8	1	2.9	8	28.6
V	2	5.1	2	5.9	3	10.7
MARITAL STATUS						
MARRIED	3	7.7	5	14.7	4	14.3
SINGLE	31	79.5	19	55.9	18	64.3
WIDOWED	1	2.6	1	2.9	1	3.6
DIVORCED	2	5.1	5	14.7	1	3.6
SEPARATED	2	5.1	0	0	1	3.6
COHABITING	0	0	4	11.8	3	10.7
LIVING CIRCUMSTANCES						
ALONE	5	12.8	15	44.1	5	17.9
WITH PARTNER	2	5.1	8	23.5	9	32.1
WITH RELATIVE	6	15.4	2	5.9	4	14.3
SUPPORTED (NOT 24HR)	4	10.3	3	8.8	1	3.6
SUPPORTED (24HR)	15	38.5	0	0	7	25.0
LONG TERM HOSPITAL	7	17.9	6	17.6	2	7.1

provided 24 hour resident staffing, at the other end of the spectrum individuals lived independently with visiting outreach support workers. Of the three subjects in the schizophrenia control group, who resided in supported accommodation, none required 24-hour residential support. However, in the co-morbid group 19 subjects lived in supported accommodation, and 15 (78.9%) of these required 24 hour residential support.

There was a significant difference in the living circumstances of the co-morbid subjects compared to schizophrenia controls ( $\chi^2=25.6$ , d.f.=5,  $p<0.001$ ). There was also a trend for the living circumstances of co-morbid subjects to be different from those of the learning disability controls ( $\chi^2=10.8$ , d.f.=5,  $p=0.055$ ). The overall impression is that co-morbid subjects are more likely to live in highly supported accommodation, the schizophrenia control group more likely to be living alone, and the learning disability control group more likely to be living with either a partner or relative.

#### 5.3.4. Employment

Controls with a mild learning disability are more likely to have been employed in a non-sheltered work placement in the course of the last five years (N=8; 28.6%), than either people with schizophrenia (N=3; 8.8%), or people with co-morbidity (N=0).

#### 5.3.5. Forensic history

There were no significant between group differences in the number offences (alleged or convicted) accrued by subjects, or the numbers of subjects in each group who had ever been charged with an offence (co-morbid N=13, learning disability N=6, schizophrenia N=13). Nine co-morbid subjects had had psychiatric court reports, five learning disability controls and eight schizophrenia controls. Two co-morbid subjects, two learning disability controls and four schizophrenia controls had been in prison, either on remand or as part of a custodial sentence. These differences between groups do not reach statistical significance.

The nature of the alleged offences is shown in table seven for each group. The two main observations when considering the distribution of offences between groups are firstly, that five subjects with schizophrenia have between them 18 “other” offences. The nature of these offences varied from bigamy to drink driving. Secondly, only one subject had committed a homicide, this female subject was in the co-morbid group.

#### 5.3.6. Alcohol and drug histories

None of the learning disability controls, but three co-morbid subjects and five schizophrenia controls have a history of drug misuse. Similarly, none of the learning disability group, but three co-morbid subjects and four schizophrenia subjects controls met RDC for alcohol dependency syndrome. These differences do not reach statistical significance.

Table seven – Forensic histories

NATURE OF OFFENCE	CO-MORBID GROUP (N=39)		SCHIZOPHRENIA GROUP (N=34)		LEARNING DISABILITY GROUP (N=28)	
	NO.	NO.	NO.	NO.	NO.	NO.
	OFFENCES	INDIVIDUALS	OFFENCES	INDIVIDUALS	OFFENCES	INDIVIDUALS
BREACH OF THE PEACE	10	7	6	5	5	3
THEFT	3	3	7	3	1	1
SHOPLIFTING	6	4	1	1	1	1
ASSAULT	10	6	9	5	4	2
EXHIBITIONISM	3	2	0	0	4	1
HOMICIDE	1	1	0	0	0	0
OTHER	3	2	18	5	1	1
TOTAL NUMBER	36	13	41	12	16	6
SPENT TIME IN PRISON		2		4		2
SPENT TIME IN SPECIAL HOSPITAL		5		4		1



The drugs of abuse in the co- morbid group comprised only two compounds, askit powders (containing substances derived from amphetamines) and cannabis. The range of drugs used in the schizophrenia control group was more extensive and included, cannabis, amphetamines, hallucinogens, sedatives and hypnotics.

#### 5.4. Discussion

##### 5.4.1.IQ

Gessler and colleagues (1989) have used the Quick Test to estimate current IQ. In a normal non-psychiatric control group, there was no difference between IQ as estimated by the NART, and IQ as estimated by the Quick IQ Test. However Frith and colleagues (1991) noted an IQ difference of 12.8-points in chronic patients with schizophrenia when current IQ is measured on the Quick IQ Test and then pre-morbid IQ measured with the NART. The NART score being the lowest. The present study concurs with this finding.

Control subjects with schizophrenia, 33 of whom completed both the Quick Test and the NART, have significantly different mean scores on these tests (paired t-test;  $p < 0.001$ ). On further analysis, the mean NART score in this group is 111.1 (s.d. 10.8) and the mean Quick IQ Test is 100.9 (s.d. 15.0). When the Quick IQ Test scores are individually subtracted from the NART scores and a mean derived, there is a 9.7 mean point discrepancy between scores. This indicates a decline in IQ between perceived pre-morbid and morbid levels in subjects with

schizophrenia alone, which is of a similar magnitude to that found by Frith and colleagues. It was not possible to make this comparison in the co-morbid group as the NART is reliant on the reading ability of the subject and some of the co-morbid group are illiterate.

#### 5.4.2.Social class

It is possible that the large number of subjects for whom paternal occupation has not been determined, in the co-morbid and learning disability groups, may represent those who would otherwise be categorised in social classes I, and II. The social class of the large numbers of controls with schizophrenia who declined to participate in the study was not determined. Ascertainment bias may therefore be operating in this sample, as those subjects from the higher social classes may be more motivated to participate in research. Therefore, given the large amount of missing data for this variable in two of the three groups and the possibility of ascertainment bias occurring in the third, the data should be interpreted with caution.

#### 5.4.3.Living circumstances

A greater proportion of co-morbid subjects require supported accommodation relative to both control groups. Once again, the possibility of ascertainment bias in the co-morbid sample should be borne in mind. It is possible that co-morbid subjects who participated in the study were more likely to take part if

support workers were on hand to reassure, encourage and introduce them to the researcher. However it could be stated that this factor may also operate in control groups and this does not appear to be the case.

#### 5.4.4. Forensic histories

Tiihonen and co-workers (1997) studied the association between specific major disorders and criminality, by prospective follow up of the 1966 Finnish birth cohort. Unfortunately, this study did not have a category for people with learning disability, but concludes that a person with schizophrenia is seven times more likely to commit a criminal offence than a member of the general population. Hodgins (1992) found that people with intellectual impairment were at a greater risk for criminal behaviour, but did not subdivide this heterogeneous category any further (Tiihonen et al, 1993). The present study does not indicate that people in the co-morbid group, with both intellectual impairment and schizophrenia, are any more likely to commit a criminal offence than subjects in either control group.

#### 5.4.5. Alcohol and substance abuse

Traditionally people with learning disability have, in the past, lived in closely supervised segregated settings. However, the move towards normalisation and integrated community care has resulted in less institutional accommodation and a greater emphasis on autonomy for this group of people. Consequently, a high degree of protection from the perceived “unhealthy “ aspects of society can no longer be ensured. It is therefore only relatively recently that the issue

of drug and alcohol abuse has been considered to be pertinent to people with learning disabilities (Christian and Poling, 1997).

There have been no large scale attempts to estimate the prevalence of substance abuse in people with learning disability, and no study has looked specifically at people with co-existing psychiatric illness. Those studies which have been conducted in this area (e.g. DiNitto and Krishef, 1983; Edgerton, 1986; Gress and Boss, 1996) derive similar conclusions. They concur that many people with learning disabilities do use alcohol and cannabis on a regular basis, although this is usually to a lesser extent than contemporaries within the general population. People with learning disabilities may also occasionally experiment with other illicit drugs e.g. LSD, cocaine and amphetamines, although such usage is still relatively rare.

The present study mirrors these results, in the control group with mild learning disability alone, none of the 29 subjects fulfilled RDC for alcohol dependency and none used illicit drugs, as far as could be determined. However in the co-morbid group both alcohol dependency and drug misuse were detected with the same relative frequency as seen in the schizophrenia control group. It is of note that the repertoire of drugs of abuse was more restricted in the co-morbid group, with only cannabis and an amphetamine derivative being used.

In a large North American catchment area study, 47% of all people with a diagnosis of schizophrenia also met DSM III-R criteria for lifetime substance

misuse disorder (Regier et al, 1990). Given the magnitude of this association, the relationship between substance misuse disorders and the onset of psychosis has been the subject of recent research (Hambrecht and Hafner, 1996). It remains unclear whether substance misuse can increase vulnerability to or initiate the onset of chronic psychoses in the absence of sustained abuse (Flaum and Schultz, 1996). In the present study polydrug abuse was described in 60% (3/5) of those control subjects with schizophrenia who had a history of drug abuse, none of these subjects stated that they were using drugs at the time the study was conducted. These figures should be considered cautiously as is known that methods reliant on subject and informant report may have serious limitations in the detection of substance misuse.

A community based study in inner London (McPhillips et al, 1997) has recently shown that when a semi-structured questionnaire for detecting drug misuse is administered to subjects and informants a significant number of false negative responses are obtained. The results of hair and urine drug screen analysis in the same sample revealed that 33% of respondents had covertly abused amphetamines, opiates or cocaine in the last three months.

### 5.5.Conclusions

The three groups of subjects are well matched for age and sex. The co-morbid group is well matched to the learning disability control group for morbid IQ, as rated by the Quick Test. Co-morbid subjects are matched to the schizophrenia

control group for hospital status and employment status. In many subjects in the learning disability control group and co-morbid index group the paternal occupation is unknown and so a clear picture of social class status is difficult to ascertain in these groups.

The co-morbid group require greater levels of accommodation support than either control groups. There are no clear differences in forensic histories between the three groups, although the schizophrenia control group appear to have a more diverse range of alleged offences than either the co-morbid or learning disability groups. It is perhaps noteworthy one co-morbid subject had been convicted of homicide. Learning disability control subjects do not appear to abuse alcohol or drugs. Co-morbid subjects use alcohol to the same degree as control subjects with schizophrenia and appear to use illicit drugs to a limited extent with a restricted repertoire relative to the control group with schizophrenia.

## **CHAPTER SIX**

### **A GENERAL CLINICAL PROFILE OF THE STUDY POPULATION**

*“ In isolated cases there was a report of inflammation of the brain in childhood, not altogether unfrequently also of head injuries.....”*

Kraepelin, 1919

#### **6.1. Introduction**

This chapter considers the clinically relevant results of the General History Questionnaire (appendix one) gathered on all subjects by case record review, clinical interview and informant interviews. Results obtained from the SADS-L semi-structured interview and the PANSS assessment of psychopathology are also presented.

#### **6.2.Method**

The General History Questionnaire was completed on all subjects (chapter six). The SADS-L and PANSS were also completed following a semi-structured clinical interview with each subject. This was generally completed at the same time as the General History Questionnaire during a single composite interview.

The coded clinical data from the General History Questionnaire, SADS-L diagnoses and PANSS were entered into an excel database and finally into SPSS. Statistical analysis was conducted using one-way ANOVA with post-hoc least significant difference test, Student's Independent t-test, Chi-Squared test, and the Mann-Whitney U Test.

## 6.3. Results

### 6.3.1. Age of onset of psychosis

In this study, the ages of first onset of psychotic symptomatology, first psychiatric consultation, first psychiatric admission, first use of antipsychotic medication and diagnosis of schizophrenia were obtained, for co-morbid index subjects and control subjects with schizophrenia. These ages were determined by reference to case notes and interviews with both subjects and their relatives. The time delay between age at first symptomatology and age at diagnosis of schizophrenia was calculated. These results are shown in table eight.

There are no significant differences between groups in any of the ages considered (t-test). When groups are split by gender the general trend is for all ages under study to be slightly earlier in men than women, however analysis both between groups and within groups shows no significant effect of gender on any of the ages under study (t-test). There are no significant differences in the time delay from age of first symptoms to age at first diagnosis either between total groups or within groups when cases are analysed by gender. These results therefore show that contrary to experimental evidence (Reiss et al, 1982), diagnostic overshadowing does not appear to be a significant factor in the diagnosis of schizophrenia in people with mild learning disability.



### 6.3.2. Time spent in hospital

The lifetime number of hospital admissions was ascertained for each subject in the co-morbid index group and the schizophrenia control group. The total number of days spent in hospital was calculated and any time spent in a special hospital or a secure hospital unit noted. There were no gender differences in either group when considering the total number of days spent in hospital. There was a significant difference in the mean number of lifetime hospitalisations between co-morbid subjects and schizophrenia controls (6.87 s.d. 4.7; 9.85 s.d. 6.73 respectively; Mann-Whitney U Test  $p=0.034$ ). However, co-morbid subjects had not spent any less time in psychiatric hospital, special hospitals or secure hospital units than schizophrenia controls. Co-morbid subjects therefore had fewer admissions, but for longer periods, than control subjects with schizophrenia.

### 6.3.3. Current service utilisation

At the time of study, 28.2% (N=11) of index co-morbid subjects and of 17.6% (N=6) of controls with schizophrenia were hospital in-patients. Considering only those subjects living in the community (N=58), the proportions receiving services from community nurses, social workers, home help and day care resources are shown in table nine. Only one subject was detained under the Mental Health (Scotland) Act 1984, this person was a control with a diagnosis of schizophrenia. This individual was being managed on a section 18 of the Act and was living in the community on leave of absence from the hospital. Significantly more subjects with co-morbidity were in receipt of services from

Table eight – Age of onset of psychosis

VARIABLE	TOTAL			MALES			FEMALES		
	MEAN	ST.DEV.	P VALUE*	MEAN	ST.DEV.	P VALUE*	MEAN	ST.DEV	P
<b>AGE OF FIRST SYMPTOMS</b>			NS			NS			NS
CO-MORBID (N=38)	24.4	10.2		23.8	9.9		25.1	10.7	
SCHIZOPHRENIA (N=32)	22.8	5.1		21.9	4.0		23.9	6.3	
<b>AGE OF FIRST CONSULTATION</b>			NS			NS			NS
CO-MORBID (N=38)	23.7	10.2		22.9	10.3		24.6	10.4	
SCHIZOPHRENIA (N=32)	22.8	6.0		21.4	5.6		24.6	6.3	
<b>AGE OF FIRST ANTIPSYCHOTIC</b>			NS			NS			NS
CO-MORBID (N=36)	28.1	9.4		27.7	8.6		28.4	10.3	
SCHIZOPHRENIA (N=26)	24.8	5.4		23.4	4.3		27.5	6.5	
<b>AGE OF FIRST ADMISSION</b>			NS			NS			NS
CO-MORBID (N=39)	25.2	11.3		23.5	10.7		27.1	11.9	
SCHIZOPHRENIA (N=33)	26.5	7.5		24.8	6.7		28.7	8.2	
<b>AGE AT FIRST DIAGNOSIS</b>			NS			NS			NS
CO-MORBID (N=36)	30.0	9.5		30.4	8.1		29.5	11.2	
SCHIZOPHRENIA (N=32)	27.8	7.8		26.2	7.9		29.8	7.3	
<b>TIME INTERVAL (SYMPTOMS TO DIAGNOSIS)</b>			NS			NS			NS
CO-MORBID (N=36)	4.9	7.3		5.9	8.7		3.8	5.4	
SCHIZOPHRENIA (N=32)	5.0	5.6		4.3	5.7		5.9	5.4	

\*T-TEST BETWEEN GROUPS (LEVEL OF SIGNIFICANCE TAKEN AS P = 0.05)

community psychiatric nurses ( $\chi^2 = 7.8$ , d.f.=1,  $p=0.005$ ) and social workers ( $\chi^2=3.82$ , d.f.=1,  $p=0.05$ ) than subjects in the schizophrenia control group.

#### 6.3.4. Use of psychotropic medication

The mean chlorpromazine equivalent doses of antipsychotic medication, at the time of assessment was calculated (Davis, 1976). There were no significant differences between co-morbid and schizophrenia control groups (583mg s.d 660; 748mg s.d. 735, respectively).

There were no differences between these groups in the numbers of subjects receiving depot antipsychotic preparations, antidepressants, lithium, or antimuscarinic medication. Similarly, there were no between group differences in the numbers of subjects who had ever received the atypical antipsychotics clozapine or risperidone.

#### 6.3.5. Deliberate self-harm

Only one learning disability control subject (4%) had ever engaged in deliberate self harm, relative to six (18.2%) co-morbid subjects and eighteen schizophrenia controls (52.9%). Co-morbid subjects are significantly less likely to deliberately self harm than people with schizophrenia and no pre-morbid cognitive impairment ( $\chi^2=11.6$ , d.f.=1,  $p=0.001$ ).

#### 6.3.6 Epilepsy, head injury and cerebral infections

Table nine - Service utilisation of all subjects with schizophrenia living in the community.

SERVICE RECEIVED	CO-MORBID GROUP (N=28)		SCHIZOPHRENIA (N=28)		PEARSON CHI-SQUARED TEST (BETWEEN GROUPS)
	NUMBER	PERCENTAGE	NUMBER	PERCENTAGE	
CURRENTLY UNDER TERMS OF MENTAL HEALTH ACT	0	0	1	4.0	NS
COMMUNITY PSYCHIATRIC NURSE	15	53.6	5	17.8	$\chi^2 = 7.8$ d.f.=1, p=0.005*
SOCIAL WORKER	9	32.1	3	10.7	$\chi^2 = 3.82$ d.f.=1, p=0.05*
ADULT TRAINING CENTRE	8	28.6	0	0	N/A
DAY HOSPITAL	9	32.1	8	28.6	NS
DAY CENTRE	4	14.3	1	4.0	NS
VOLUNTARY AGENCY	2	7.1	1	4.0	NS
HOME HELP	3	10.7	2	7.1	NS

These results are presented in table ten. Co-morbid subjects are more likely to have a history of epilepsy than people with schizophrenia ( $\chi^2= 16.2$ , d.f.=1,  $p<0.001$ ), but not control subjects with learning disability. Co-morbid subjects are more likely to have been seizure free in the last 5 years than learning disability controls ( $\chi^2= 6.1$ , d.f.=1,  $p=0.013$ ). There are no differences in the age of first onset of epilepsy between these two groups. In the majority of subjects in both groups, the aetiology of epilepsy is considered to be idiopathic. A slight excess of male subjects is present amongst those people with epilepsy in both the co-morbid and learning disability groups (64.7% and 62.5% respectively).

Focusing on the co-morbid subjects, there are no inter-group differences between those subjects with and without epilepsy when the number of psychiatric hospital admissions, total time in hospital, mean ages of onset, admission, consultation, diagnosis of schizophrenia and first antipsychotic administration are considered. In addition, no differences are seen in terms of the dose of chlorpromazine equivalent medication received at the time of assessment, number of deliberate self harm acts or alleged criminal offences.

Five co-morbid subjects and four learning disability controls have a history of either meningitis, encephalitis, or head injury associated with loss of consciousness. None of the control subjects with schizophrenia have a history of any of these conditions.

Table ten - Past medical history

CONDITION	1 CO-MORBID (N=39) N (%)	2 SCHIZOPHRENIA (N=34) N (%)	3 LEARNING DISABILITY (N=28) N (%)	$\chi^2$ Test 1 vs.2 1 vs.3
HISTORY OF EPILEPSY	17 (43.6)	1 (2.9)	9 (32.2)	p<0.0001
AETIOLOGY OF EPILEPSY				
IDIOPATHIC	11(28.2)	1 (2.9)	5 (17.9)	NS
FEBRILE CONVULSIONS	2(5.1)		1 (3.6)	
TRAUMA	2(5.1)		2 (7.1)	
MEDICATION	1(2.6)			
UNABLE TO ASCERTAIN	1(2.6)		1 (3.6)	
FREQUENCY OF SEIZURES				
DAILY				
> 2 / WEEK				
WEEKLY			2 (7.1)	
2-4 / MONTH	1 (2.6)		1 (3.6)	
MONTHLY	1 (2.6)		1 (3.6)	
< 12 / YEAR	1 (2.6)		2 (7.1)	
YEARLY				
>YEARLY	1 (2.6)	1 (2.9)		
NONE FOR > 5 YEARS	13 (33.3)		2 (7.1)	p=0.013
UNABLE TO ASCERTAIN			1 (3.6)	
HISTORY OF MENINGITIS	2 (5.1)	0	3 (10.7)	NS
HISTORY OF ENCEPHALITIS	1 (2.6)	0	0	NS

#### 6.3.7 Psychopathology at time of study

These results are presented in table eleven. A one-way ANOVA indicates that highly significant differences exist between the three subject groups in all four major categories of the PANSS i.e. negative, positive, general and total symptoms. Using a post-hoc least significant difference test, the co-morbid group have significantly more negative symptoms, but show no differences in positive, general or total symptom profiles compared to the schizophrenic control group. The mild learning disability control group show significantly fewer symptoms in all four categories relative to the other two groups. There are no significant correlations between positive and negative symptom profiles and Quick IQ scores in any of the three groups.

The individual components of the PANSS were then considered in subjects with a diagnosis of schizophrenia, using an independent t-test, to examine between group differences. Co-morbid subjects were rated as having fewer delusions ( $p<0.05$ ), less suspiciousness and persecution ( $p<0.05$ ), more difficulty in abstract thinking ( $p<0.001$ ), less spontaneity in conversation ( $p<0.01$ ) and more stereotyped thinking ( $p<0.001$ ) than controls with schizophrenia. In terms of the general symptom profile, co-morbid subjects were rated as having poorer attention ( $p<0.01$ ), lacking judgement and insight ( $p<0.05$ ), having less impulse control ( $p<0.001$ ) and showing more preoccupation ( $p<0.05$ ) than controls with schizophrenia alone. When the two groups with schizophrenia are further sub-divided by gender, there are no differences between male and females for each of the four sub-categories

Table eleven – Psychopathology at time of assessment as rated by the PANSS

VARIABLE	SCHIZOPHRENIA AND MILD LEARNING DISABILITY (MEAN AND 95% C.I.)	SCHIZOPHRENIA (MEAN AND 95% C.I.)	MILD LEARNING DISABILITY (MEAN AND 95% C.I.)
PANSS	(N=39)	(N=32)	(N=24)
POSITIVE SYMPTOMS (N. RANGE 7-49)	12.6 (10.8-14.4)	14.0 (12.0-16.0)	7.6** (7.1-8.0)
NEGATIVE SYMPTOMS (N. RANGE 7-49)	23.3** (20.5-26.2)	18.3** (15.3-21.3)	9.2** (8.0-10.3)
GENERAL SYMPTOMS (N. RANGE 16-112)	30.8 (27.1-34.4)	27.9 (25.1-30.7)	19.1** (17.6-20.6)
TOTAL SYMPTOMS (N. RANGE 30-210)	66.3 (59.0-73.5)	60.2 (53.5-66.8)	35.5** (33.0-37.9)

(One- way ANOVA with post-hoc LSD)

\* p < 0.05 relative to both other groups.

\*\* p < 0.01 relative to both other groups.



of the PANSS in the co-morbid group. However, in the schizophrenia control group males have significantly more positive symptoms ( $p=0.01$ ), negative symptoms ( $p<0.05$ ) general symptoms ( $p<0.01$ ), and total symptoms ( $p<0.01$ ) than females within the same group. These results are tabulated in table twelve.

Each of these two groups was further analysed to seek any associations between age of onset of symptoms or age at first admission, relative to symptom profiles as rated by the PANSS. Using a Spearman's correlation co-efficient both within groups and between groups, no significant correlations were found between these ages and the four symptom profiles.

No correlations were found between total number of days spent in psychiatric hospital and PANSS symptom profile scores in the co-morbid group. However, in the schizophrenia control group there was a significant positive correlation (Spearman's  $\rho$  0.384,  $p=0.033$ ) between total number of days spent in psychiatric hospital and positive symptom scores at the time of assessment. This relationship is shown graphically in figure one.

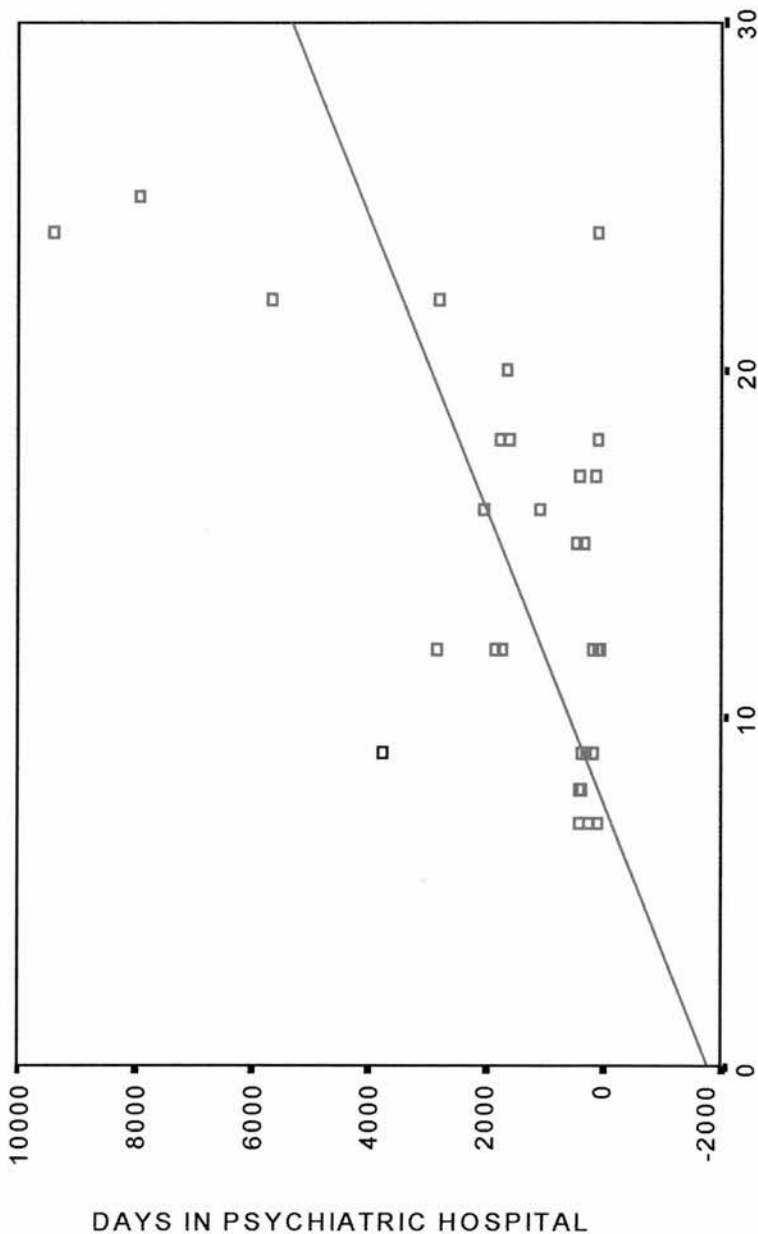
The co-morbid group and schizophrenia control group were divided into those receiving depot antipsychotic medication and those receiving oral antipsychotic medication. There were no significant differences seen (t-test) between the positive, negative or total PANSS scores within groups in people taking parenteral or oral antipsychotic medication

Table twelve – Mean PANSS ratings in co-morbid and schizophrenia groups by gender.

VARIABLE	SCHIZOPHRENIA AND MILD LEARNING DISABILITY  MALE (N = 21) (MEAN AND S.D)	SCHIZOPHRENIA AND MILD LEARNING DISABILITY  FEMALE (N = 18) (MEAN AND S.D.)	SCHIZOPHRENIA  MALE (N = 17) (MEAN AND S.D.)	SCHIZOPHRENIA  FEMALE (N = 15) (MEAN AND S.D.)
PANSS				
POSITIVE SYMPTOMS (N. RANGE 7-49)	13.0 (6.4)	12.2 (4.3)	16.3 (6.1)**	11.4 (3.7)**
NEGATIVE SYMPTOMS (N. RANGE 7-49)	23.8 (8.2)	23.1 (9.5)	21.5 (8.7)*	14.7 (6.4)*
GENERAL SYMPTOMS (N. RANGE 16-112)	30.5 (10.2)	31.1 (12.6)	31.3 (8.2)**	24.0 (5.0)**
TOTAL SYMPTOMS (N. RANGE 30-210)	66.1 (21.7)	65.8 (23.7)	69.1 (19.5)**	50.1 (11.0)**

Independent t-test within groups.  
 \* p < 0.05.      \*\* p < 0.01.

Figure one – Correlation with PANSS positive symptom score and total number of days spent in psychiatric hospital : Schizophrenia control group.



POSITIVE SYMPTOM SCORE (AS RATED BY PANSS)

SPEARMAN'S rho = 0.384

Focusing specifically on the co-morbid group, subjects were divided into two sub-groups those with a history of epilepsy (N=17) and those without (N=22). An independent t-test was then performed between these two groups for each of the four symptom profiles of the PANSS. No significant differences were seen between mean symptom profile scores (positive, negative, general and total symptoms) and those people in the co-morbid group with epilepsy and those without.

#### 6.2.8 Psychiatric diagnoses (lifetime)

All co-morbid and schizophrenia subjects met at least one of three criteria for schizophrenia. Each individual was rated for DSM-III-R criteria, R.D.C. and St. Louis (Feighner) Criteria. 37 co-morbid subjects and all schizophrenia subjects fulfilled definite RDC for schizophrenia. 35 co-morbid subjects fulfilled definite Feighner Criteria and a further 2 fulfilled probable Feighner Criteria. 29 schizophrenia controls fulfilled definite and 5 fulfilled probable Feighner Criteria. 37 co-morbid subjects and all 34 schizophrenia controls met DSM III-R Criteria.

Additional psychiatric diagnoses were derived from the SADS-L. This could not be completed for four learning disability controls where there were no casenotes available and the subject's own account was considered unreliable. Primary, secondary and tertiary SADS-L diagnoses are shown in table thirteen. No subject fulfilled more than three diagnoses on the SADS-L.

Table thirteen - SADS-L psychiatric diagnoses

SADS-L DIAGNOSES PRIMARY(1 <sup>o</sup> ) SECONDARY (2 <sup>o</sup> ) TERTIARY (3 <sup>o</sup> )	CO-MORBID (N=39)			SCHIZOPHRENIA (N=34)			LEARNING DISABILITY(N=28)		
	1 <sup>o</sup>	2 <sup>o</sup>	3 <sup>o</sup>	1 <sup>o</sup>	2 <sup>o</sup>	3 <sup>o</sup>	1 <sup>o</sup>	2 <sup>o</sup>	3 <sup>o</sup>
SCHIZOPHRENIA	37			34					
SCHIZOAFFECTIVE DISORDER	1								
MAJOR DEPRESSIVE DISORDER		2			1		1		
MINOR DEPRESSIVE DISORDER					2		2		
BIPOLAR DISORDER		1							
ALCOHOL DEPENDENCY		4			3	1			
DRUG USE DISORDER		1			1				
PANIC DISORDER					2		1		
GENERALISED ANXIETY DISORDER		3			1	1	1	1	
OBSESSIVE COMPULSIVE DISORDER					1				
PHOBIC DISORDER					2				
OTHER DISORDER	1	2	2				1		
NO DISORDER	0	26	37		0	22	32	18	23
UNASCERTAINED							4	4	4

## 6.3. Discussion

### 6.3.1. Age of onset

Quantitative assessment of the age of onset of a psychotic illness is often difficult to determine in retrospect (Beiser et al, 1993). Even when studying individuals at high risk for schizophrenia and people seen during the first episode of illness, recall bias is a potential confounder (Maurer and Hafner, 1995).

Determining the age of onset of schizophrenia in people with pre-existing cognitive impairment may have additional methodological problems. During the prodromal stage of a schizophrenic illness early, subtle behavioural changes, may herald the initial phase of illness. In some people these changes may be incorrectly attributed, by caregivers, relatives or health professionals, to the person's learning disability per se i.e. diagnostic overshadowing occurs (Reiss and Szyszko, 1983).

It has been suggested that the development of schizophrenia in children and adolescents (juvenile onset) is associated with pre-morbid motor and language impairments (Hollis, 1995; Hoff et al, 1996). Furthermore, Alaghband-Rad and colleagues (1997) have hypothesised that, when the age of onset of schizophrenia is less than 12, there may be a potent neurobiological basis for the illness that is characterised by an excessive of negative symptomatology. The longer term outcome of early onset cases has been reported as poor at 7

year follow up, in terms of social competence and residual symptoms of psychosis, when compared to later onset controls (Schmidt et al, 1995)

However, the extent to which the early development of a schizophrenic illness in itself impairs the ability of an individual to mature socially is not addressed by Schmidt and colleagues. It remains undetermined as to whether the poor outcome reported is a consequence of early onset per se, or an intrinsic pathological process. In a prospective 5 year follow up study of patients admitted to hospital with a diagnosis of schizophrenia no relationship was found between measures of outcome and age at onset (Wieselgren and Lindstrom, 1996). However, scholastic difficulties in childhood and poor pre-morbid adjustment were stated to be predictors of poor outcome in their study cohort.

Although the co-morbid group show more negative symptomatology than the schizophrenia control group, there is no evidence that the age of onset of schizophrenia is any earlier in the co-morbid group. Nor is there any evidence, in this relatively small sample, that any relationship exists between age of onset of illness and negative symptoms or the total number of days spent in psychiatric hospitals in these two age and sex matched groups.

In this study, the general trend is for men to become ill before women, in both the co-morbid and schizophrenia control groups, although this finding does not reach significance and the numbers involved are small in epidemiological

terms. Numerous studies have concluded that male patients with schizophrenia have an earlier age of onset than females (e.g. Faraone et al, 1994). However, it has recently been suggested that this gender difference may not be a robust biological characteristic of schizophrenia, but might be a function of a failure to control for marital status and pre-morbid personality when making male / female comparisons of age of onset (Jablensky and Cole, 1997). These factors were not controlled for in the data analysis of the present study.

### 6.3.2. Service utilisation

When considering issues of service utilisation by the co-morbid group continuity of care is of importance. The psychiatric careers of many of the co-morbid subjects have been split between general adult psychiatry service providers and learning disability service providers. This has arisen as the co-morbid diagnosis of mild learning disability and schizophrenia has fallen within the remit of both services at differing chronological points in both the subject's history and the evolution of modern day service provision.

Those subjects in the co-morbid group who lived in the community were more likely to be receiving the services of a community psychiatric nurse or social worker than control subjects with schizophrenia, despite living in supported accommodation. This increased level of community support provided to the co-morbid group does not appear to be a function of more extensive forensic, self harm, drug and alcohol histories, current detention under the Mental Health



Act, or additional psychiatric diagnoses, relative to the schizophrenia control group.

Although no difference is apparent in the total number of days spent in hospital between co-morbid subjects and schizophrenia controls, co-morbid subjects do have fewer admissions of longer duration. There is no relationship in the co-morbid group between symptom profiles at the time of assessment and the total number of days they have spent in hospital. However, in the schizophrenia control group there is a positive correlation between positive symptoms at assessment and total number of days spent in psychiatric hospital. Given that co-morbid subjects have the same mean number of positive symptoms as schizophrenia controls subjects, it is perhaps surprising that schizophrenia controls receive a reduced level of community support (in terms of supported accommodation, community nurses and social work input). It could be hypothesised that the reasons for a reduced level of community support in the controls with schizophrenia are linked to poor compliance with treatment and limited insight. However in these circumstances, it would be expected that more than one subject would be managed using the provisions of the Mental Health Act. Alternatively, such patients with residual positive symptoms living in the community may constitute a treatment resistant group who require relatively frequent in-patient admissions.

The combination of an increased need for community support and pattern of fewer, yet longer admissions in the co-morbid group, may be indicative of a

different or more treatment resistant form of illness. Alternative explanations may be that this finding is a consequence of poor continuity of care, differing policies between service providers, or simply the need for complex packages of care to be provided for longer periods of time amongst this group. This latter point was evident even in the pre-community care era. Johnstone and colleagues (1981) determined that cognitive impairment in patients with schizophrenia was one of the most important factors in determining whether patients progressed to long term care in hospital or were able to live in the community.

In an Edinburgh based study of service utilisation by people with schizophrenia over a six month period, Lang and colleagues (1997) have shown no relationship between use of services (with the exception of in-patient and day hospital facilities) and mental state. Although stated that it was not the most unwell or disabled of the patients who had been in contact with the greatest number of services over the six month period, people with co-morbid learning disability were excluded from the study cohort. The present study suggests that both the community and admission profiles for co-morbid subjects are different to those people with schizophrenia alone. Many co-morbid subjects remain within the remit of general adult, as opposed to learning disability, services. Although an economic evaluation of service provision in the co-morbid group was not conducted in this study, this would be of interest in the future. Perhaps the current level of cognitive ability is more important than current mental state in determining the use of psychiatric services of people with schizophrenia.

### 6.3.3. Medication

25% of people with learning disabilities routinely receive antipsychotic drugs, in the majority the indication for treatment is the control of challenging behaviour. (Branford, 1996). Antipsychotic induced dyskinetic movements are recognised as occurring commonly in people with learning disabilities (Sachdev, 1992). This has led to recent interest in studies of cessation of antipsychotic medication in people with learning disabilities and behavioural difficulties (Branford, 1996).

In the present study, neither the mean chlorpromazine equivalent dose at the time of assessment, nor the numbers of subjects receiving antimuscarinic medication are any different between co-morbid subjects and schizophrenia controls. The use of clozapine in treatment resistant co-morbid patients has been shown (albeit in only a small numbers) both to improve quality of life measures (Pary, 1994) and psychopathology ratings (Sajatovic et al, 1994).

In a small number of co-morbid patients, risperidone has been shown to reduce extra-pyramidal side-effects when substituted for conventional antipsychotic agents (Simon et al, 1996). There are no differences in the co-morbid group and schizophrenia control group in terms of those patients who have been given a trial of either of these novel antipsychotic agents. The high numbers of subjects in the co-morbid group with an additional diagnosis of epilepsy – a contra-indication to treatment with clozapine (if the epilepsy is uncontrolled),

and cautioned with risperidone treatment (British National Formulary, 1997) may account for this finding.

#### 6.3.4. Deliberate self harm

Suicidal behaviour is an under reported phenomenon in people with learning disabilities and co-morbid psychiatric disorders (Walters et al, 1995). A meta-analysis of the available literature by Harris and Barraclough (1997) concludes that virtually all mental disorders, except learning disability and dementia, have an increase risk of completed suicide. However, from this report it is not clear if people with co-morbid learning disability and schizophrenia have an increased risk of suicide relative to the general population or what the frequency of deliberate self harm behaviour is in this group.

A recent Scandinavian study reported that 7% of all suicides over a 12 month period in Finland were in people previously identified as suffering from schizophrenia (Heila et al, 1997). Patients with schizophrenia with high negative symptom scores are reported to have a reduced incidence of both completed suicide and reported suicidal ideation (Fenton et al, 1997). Whereas, the reverse is the case for patients with schizophrenia and good insight into their illness, irrespective of the symptom profile they display (Amador et al, 1996).

The present study has shown that people with schizophrenia and mild learning disability are less likely to have engaged in deliberate self harm than people

with schizophrenia and no learning disability ( $p=0.001$ ). This finding is consistent with what is known about suicidal behaviour in people with learning disability and also people with schizophrenia. The co-morbid group have more negative symptoms than schizophrenia controls and less insight into their illness as rated by the PANSS. It has been shown that the higher a person's IQ, the greater insight they may be expected to have into their own schizophrenia illness (David et al, 1995). For these reasons and also because people with learning disability rarely deliberately self harm, the schizophrenia control group may be considered to be at greater risk of self harm than co-morbid subjects. However, as the results of this study show, the risk of self harm in the co-morbid group is far from negligible and it is greater than expected in people with learning disabilities and no evidence of schizophrenia.

#### 6.3.5. Epilepsy

In the current study a history of epilepsy is more commonly found in both co-morbid and learning disability subjects than those subjects with schizophrenia alone. However, it is known that like people with mild learning disability, people with epilepsy develop schizophrenia at a rate exceeding that seen in the normal population (Hyde and Weinberger, 1997).

In the co-morbid group those people with seizure disorders do not stay in psychiatric hospital any longer than those without seizure disorders. This concurs with the findings of Pary (1993b), who found no differences in

hospitalisation times of people with and without seizure disorders who had co-morbid mental retardation, of mixed severity, and psychiatric disorder.

There are no differences in the perceived aetiology of the epilepsy between groups, the majority of all cases are idiopathic. The age of onset of epilepsy is no different between the co-morbid group and learning disability control group. A connection between temporal lobe epilepsy and schizophrenia has been suggested by a number of investigators ( e.g. Stevens, 1988 (review)). Using this model it has been suggested that an early age of onset of epilepsy may be associated with the subsequent development of schizophrenia (Roberts et al, 1990). In a study of 62 people with all types of epilepsy and co-morbid schizophrenia, compared to age and sex-matched controls with epilepsy and no schizophrenia, Mendez et al (1993) found a later age of onset of epilepsy in the group with schizophrenia. Neither of these relationships are substantiated by the present study. This study did not attempted to subdivide the types of epilepsy seen in individuals, due to the inaccuracy of making retrospective diagnoses of this nature when EEGs are not always available.

There is a significant difference in the current frequency of seizures between groups. A third of the co-morbid group (N=13) are people with a history of epilepsy, who have not had a seizure in the last five years, relative to 7.1% (N=2) of the learning disability group ( $p=0.01$ ). This is perhaps surprising given that the co-morbid group are receiving epileptogenic antipsychotic medication, in a mean daily dose of 583mg, and the learning disability group are not. As

the learning disability group also derive from a population who have been, or are in contact with hospital services, this finding is unlikely to be the result of the co-morbid group having greater contact with services, with the consequence that their epilepsy is better controlled.

Alternatively, this finding may represent selection bias, the learning disability control group may be in contact with services as a consequence of intractable epilepsy.

The current frequency of seizures may be of importance in distinguishing those people with learning disability and epilepsy who develop schizophrenia from those who do not. The phenomenon of "forced normalisation" has been described in relation to the schizophreniform psychoses of epilepsy (Trimble, 1996), whereby a reduction in seizure activity following the introduction of anticonvulsant agents is associated with an exacerbation of psychotic symptomatology. It is possible that a similar mechanism may be of aetiological significance in the co-morbid population, where cerebral dysfunction as evidenced by epilepsy, is contributing to the combined conditions of learning disability and schizophrenia.

#### 6.3.6. Cerebral infection

A recent epidemiological survey of 11,017 subjects in the 1966 North Finland birth cohort found that four cases of schizophrenia (out of a total of 76) had suffered a childhood viral CNS infection. The odds ratio of developing

schizophrenia after such an infection was calculated as 4.8, other significant risk factors being a low IQ (<85), perinatal brain damage and male gender (Rantakallio et al, 1997). It is therefore of interest that in this study none of the schizophrenia control group had a history of either childhood meningitis or encephalitis, However, 3 subjects in each of the co-morbid group and learning disability control group had a history of childhood meningitis. One subject in the co-morbid group had a history of childhood viral encephalitis. Although these differences between groups do not reach statistical significance, the relative rarity of such illnesses in the general population (145 / 11017 people had suffered a childhood CNS infection in the Finnish 1966 birth cohort study), makes their detection in the co-morbid and learning disability control populations noteworthy.

#### 6.3.7. Head Injury

Wilcox and Nasrallah (1987) demonstrated that from examination of medical notes it could be established that patients with schizophrenia were significantly more likely to have had a history of head trauma requiring medical attention, before the age of ten, than affective or surgical control patients. However, in their sample of 268 cases of first-episode schizophrenia, Johnstone and colleagues (1987) found only one case in which a history of previous head injury appeared relevant to the mental state. There are no significant differences between groups in the present study in the number of subjects who have reported a head injury with associated loss of consciousness. In the relatively small sample of subjects with schizophrenia and no learning disability



in this study, none report a head injury with loss of consciousness, However, three co-morbid subjects have experienced such head trauma and one learning disability subject.

#### 6.3.8. Psychopathology

It has been suggested that positive and negative symptoms in schizophrenia may be indicative of distinct pathophysiologies (Strauss et al, 1974; Crow, 1980) This has led to the development of rating scales for the quantitative assessment of these specific symptom profiles (e.g. PANSS). Positive symptoms are generally required in current classification systems to make a diagnosis of schizophrenia (e.g. R.D.C. and DSMIII-R). It has been suggested that the incorporation of negative symptom requirements into classification systems weakens construct validity, as processes previously considered central to the diagnosis (i.e. positive symptoms) may be minimised in such a schema (McGlashan and Fenton, 1992).

The main finding of the present study is that co-morbid subjects have more negative symptoms than schizophrenia controls. Other studies have shown relationships between increased negative symptomatology and poor general pre-morbid functioning (e.g. Keefe et al, 1989; Andreasen et al, 1990; Buchanan et al, 1990;), poor pre-morbid social adjustment (Addington and Addington, 1993; McCreadie et al, 1994), low IQ (Johnstone et al, 1978; Kay et al, 1986), or low scores on tests of cognitive functioning (Owens and Johnstone, 1980; Andreasen et al, 1981). Conversely, there have been studies

which show no association between low IQ and negative symptomatology in patients with schizophrenia (Bilder et al, 1985; Green and Walker, 1986; Walker et al, 1988;). A main criticism of these studies is that none included subjects with pre-morbid or morbid IQ's within the learning disability range.

It has been suggested that subjects with a low IQ may not be operating across the full range of cognitive abilities, hence their level of functioning is insufficient to sustain complex symptomatology (Nelson et al, 1990). Reid (1989b) is more specific in this regard, he states that ideas of influence, control and made experiences, may be particularly difficult for a person with learning disabilities to describe in conceptual terms.

In the present study, the co-morbid group are rated as having fewer delusions and less suspiciousness and persecutory ideation than the schizophrenia control group using the PANSS, but the co-morbid group have greater difficulty in abstract thinking ( $p < 0.001$ ). It may therefore be hypothesised that the co-morbid subjects show fewer delusions as a consequence of limited expressive abilities. However, this view is not substantiated by correlational data.

No significant correlations are found in either the co-morbid or schizophrenia group between IQ and positive or negative symptom scores. Within the co-morbid group, there are no significant correlations (Pearson Correlation Coefficient) between delusion ratings and ratings of difficulty in abstract thinking, or lack of spontaneity and flow of conversation. However, there are positive

correlations in the co-morbid group between ratings of delusions, conceptual disorganisation ( $p<0.01$ ) and hallucinatory behaviour ( $p<0.01$ ).

This would suggest that the ability of a subject to express delusional material is not related to abilities of abstraction or verbal abilities within this group of people, with only a mild degree of learning disability. This concurs with the work of Meadows and colleagues (1991) who also found co-morbid subjects to have less persecutory ideation than controls with schizophrenia alone. Using the SADS-L, these investigators established that standardised interviews and criteria for schizophrenia could be readily applied to people with mild learning disability and schizophrenia.

It has been suggested that the psychiatric diagnostic process in people with learning disabilities may be impeded by the phenomenon of “psychosocial masking” (Sovner, 1986). It is proposed that people with developmental disabilities may have a reduced range of life experiences relative to contemporaries in the normal population and that this may contribute to a “bland” clinical presentation of psychiatric illness. This hypothesis will be further tested when considering the adaptive behaviour rating of the co-morbid group, but would be expected to be more pertinent to a more severely learning disabled group of subjects than people with an IQ of 50-70, many of whom are able to read and write.

#### 6.3.9. Psychiatric diagnoses (lifetime)

The reliability of psychiatric classification systems, designed for use in the general population, when applied to people with learning disability without modification, is a controversial area (Sturmey, 1995). Operationalised criteria (e.g. R.D.C., D.S.M. and St. Louis Criteria) have not been systematically evaluated in a population with learning disabilities (Sturmey et al, 1991). The use of these classifications for the diagnosis of schizophrenia was therefore considered by this study. Only two co-morbid subjects did not meet DSMIII-R criteria for schizophrenia. The principle reasons for this were the presence of predominately persecutory delusions, in the absence of auditory hallucinations or formal thought disorder.

13 co-morbid subjects had additional psychiatric diagnoses as rated by the SADS-L, 2 of these subjects had a total of three psychiatric diagnoses. These were schizophrenia, alcohol dependency and antisocial personality disorder in one subject and schizophrenia, generalised anxiety state and post-ictal behavioural disturbance in the other. The two subjects with a secondary diagnosis 'listed as other' disorder had schizophrenia with pica and schizophrenia with epileptiform psychosis, respectively. This latter diagnosis was made in addition to schizophrenia as the subject showed affective change with mood congruent symptoms as a prodrome to seizures, interictal features of schizophrenia appeared to be separate and distinct from these episodes. In the one subject in the co-morbid group where a primary R.D.C. diagnosis of schizophrenia could not be made, the primary diagnosis was that of a paranoid state.

17 co-morbid subjects have major diagnoses on three of the axial classifications of DSM-III-R i.e. schizophrenia (axis I), mild learning disability (axis II), epilepsy (axis III). As demonstrated in table 13, many of these subjects also have secondary and in some cases tertiary diagnoses of axis I. The social support required by these subjects is greater than those in the schizophrenia control group. It is therefore suggested that their axis IV (severity of psychosocial stressors) and axis V (global assessment of functioning) ratings will be lower than schizophrenia controls. These variables will be considered in more detail when adaptive behaviour ratings are discussed (chapter eleven). It therefore can be seen that much relevant information may be derived from using a multi-axial classification system in the co-morbid group, more of whom have axis II and III diagnoses than the schizophrenia control group.

#### 6.4. Conclusions

The co-morbid subjects in this study have the same age of onset as schizophrenia as controls. They have fewer, yet longer admissions to psychiatric hospitals and require more general community support. This appears to be more a consequence of a combination of lowered IQ and poor social background, than symptom clusters, forensic history, substance misuse, or deliberate self harm. Learning disability controls require a similar level of support and have equivalent IQ's, social backgrounds and histories of epilepsy.

Co-morbid subjects are prescribed the same antipsychotic types and equivalent doses as people with schizophrenia and no learning disability. Yet, they have more negative symptoms, which do not appear to be related to lowered IQ, and many have a history of idiopathic seizures, although not in the last five years.

R.D.C., St.Louis Criteria and DSMIII-R Criteria may all be applied to confirm the diagnosis of schizophrenia in people with mild learning disability. However, a multi-axial system of classification, such as that provided by DSM-III-R, is of greater value in defining the complex needs and psychosocial circumstances of many of these individuals.

## CHAPTER SEVEN

### MEMORY FUNCTION IN THE STUDY POPULATION.

*“Retention is often quite well preserved. Gregor found in his experiments very dissimilar values for successive repetitions in consequence of great wavering of attention. Mistakes and senseless combinations were not corrected, but rather showed an inclination to become established.”*

Kraepelin, 1919

#### 7.1 Introduction

##### 7.1.1 Models of memory

The first systematised experiments of memory are attributed to Jacobs (1887). By giving subjects a number of word lists of increasing lengths to recall, Jacobs defined the memory span as being the longest list recalled by the subject in the correct order. He observed that the memory span of each person varied according to three parameters; the age of the subject, the nature of the material used and the ‘natural ability’ of the individual (Hulme and Mackenzie, 1992).

In more recent years, the work of Broadbent (1958) focused empirical research interest on the development of tangible models of memory. The seminal work of Atkinson and Shiffrin (1968) was the first to sub-divide the concept of memory into three distinct stores; the sensory store, the short term memory and the long term memory.

The influential theory of a working memory was proposed by Baddeley and Hitch (1974; Baddeley, 1986). The working memory acts as a short term holding store for a limited number of items for approximately 30 seconds.

During this time, information required for comprehension, and reasoning may be manipulated. Hence, working memory comprises a set of systems able to hold information temporarily, during the performance of a cognitive task e.g. reading / writing (verbal memory), drawing (visuo-spatial memory). Unlike short term memory, working memory is not regarded as a unitary system but a dynamic interacting set of sub-systems. The majority of information held in working memory is disregarded. Selected information may be 'rehearsed' via a secondary 'articulatory loop', of limited capacity, and then either disregarded or encoded in secondary / longer term memory.

Long term or secondary memory may be construed as comprising two main components, episodic memories and semantic memories (Tulving and Donaldson, 1983). Episodic memories are an individuals recollection of events that he/she has personally experienced, such as autobiographical details, or what happened yesterday. Semantic memories comprise material facts which are unrelated to specification of time or place e.g. the capital of Bolivia or the anatomical relations of a cranial nerve.

Short term memory performance may be improved by the use of rehearsal and organisational strategies, but cannot be extended beyond system limits ( Craik, 1970). In contrast, the storage capacity of the long term or secondary memory is theoretically without constraint.



The advent of functional neuroimaging studies has enabled the neuroanatomy of episodic memory to be investigated. These have suggested that efficient episodic encoding is associated with enhanced activity in the left prefrontal cortex and retrieval is associated with right-sided prefrontal activity (Fletcher et al, 1997). The low spatial resolution of functional imaging investigations of the hippocampus and associated structures has limited our knowledge of the role of this area in memory. However, lesion studies in rats, primates and man continue to emphasise the important role of the medial temporal lobe area in short term memory ability (Squire, 1992).

#### 7.1.2 Memory in people with learning disabilities

Following on the work of Jacobs, Francis Galton measured the memory span of 'feeble-minded' people and found it to be lower than that expected in the normal population. Most recent research in this area has focused on people with moderate learning disabilities and it is not known to what extent this is generalisable to people with mild learning disabilities. However, short term memory deficits are seen in people with moderate learning disabilities. Such deficits do not appear to relate to a reduction in capacity of the short term system, but more to the inability of people with learning disabilities to utilise strategies of rehearsal and organisation effectively (Belmont and Butterfield, 1969). Two main mechanisms seem to account for these difficulties.

Firstly, there is evidence that people with learning disabilities are less able than normal people to recode information presented in one sensory modality into

another e.g. to recode visually presented information into a temporal or verbal code (O'Connor and Hermelin, 1973). If information cannot be reordered into a verbal representation it is not possible to use verbal rehearsal in the articulatory loop of working memory.

Secondly, basic cognitive deficiencies e.g. dyslexia, dysarthria, restricted lexicon, may result in an inability to utilise rehearsal and organisational strategies optimally.

In normal children short term memory improves with chronological age. This may be a reflection of the ability to utilise strategies more effectively based upon trial and error learning. It is possible to train people with learning disabilities to use active memory strategies for specific tasks such that their performance is equal to that of mental age matched normal subjects (Belmont and Butterfield, 1971).

### 7.1.3 Memory in people with schizophrenia

It has been established that people with severe and enduring schizophrenia perform poorly on neuropsychological test batteries (e.g. Klonoff et al, 1970; Kolb and Wishaw, 1983; Taylor and Abrahams, 1984). There has been a relatively consistent failure to find a distinct neuropsychological profile that characterises schizophrenia (Elliot and Sahakian, 1995). However, it may be possible to distinguish patients with schizophrenia from patients with affective disorder, who may also show a degree of neuropsychological deficit, by

detailed study of the profile of impairments seen and the associations between these impairments and psychopathology (Goldberg et al, 1993b; Doody et al, 1998).

Memory function in schizophrenia has been extensively studied. One of the early reports in this field indicated that people with schizophrenia performed better on tests of recognition memory than on recall memory (Bauman and Murray, (1968) and this has since been replicated by other investigators (Koh, 1978; Goldberg et al, 1989).

More recently, it has been suggested that the memory impairments seen in schizophrenia may be more extensive than previously recognised and not confined to people who have been ill for a long period of time (McKenna et al, 1990). The nature of this widespread impairment has been likened to the classical amnesic syndrome (Tamlyn et al, 1992), of intact short term memory with wide ranging deficits in long term memory (Baddeley, 1982). This pattern of deficits is typically seen in Korsakoff's psychosis and bilateral medial temporal lobectomy patients. It is quite different to the impairment of both short and long-term memory functions seen in patients with Alzheimer's disease. Heaton and colleagues (1994), using a case controlled approach, concur that the pattern of neuropsychological impairments seen in people with schizophrenia is quite different to that seen in people with progressive cortical dementias.

However, in addition to a pattern of deficits resembling the classical amnesic syndrome, patients with schizophrenia also show slower semantic memory processing and a tendency to make more mistakes on simple tasks of verification (Tamlyn, 1992). It is possible that these findings are representative of the prefrontal-type of cognitive deficit described in people with schizophrenia (i.e. Goldberg et al, 1987) rather than temporal lobe pathology per se.

In a study of 24 monozygotic twins discordant for schizophrenia a neuropsychological profile consistent with frontal lobe and medial temporal lobe dysfunction was found in affected probands relative to their well co-twin and control twin pairs (Goldberg et al, 1993c). Short-term memory deficits were apparent in story recall, visual recall and paired associate learning but recognition memory remained relatively intact. Effortful lexical retrieval, measured by verbal fluency, was also impaired, but procedural learning of a motor skill preserved. The authors argue that the differences seen in the affected twins can not be attributed to differences in the genome, family environment, socio-economic circumstances or educational opportunities of these individuals. Therefore they conclude that these impairments appear to be related to the intercession of the disease. The mechanisms by which this may occur have been hypothesised by other investigators as either inefficient encoding (Koh and Peterson, 1978) or inefficient retrieval (McClain, 1983). However, additional confounders have been identified which need to be considered further before memory impairment may be considered to be intrinsic to schizophrenia (Tamlyn et al, 1992).

Returning firstly to the seminal work of Jacobs (1887), age, IQ (natural ability), and the nature of the material to be remembered are all potential confounders. There are no relationships discernible between neuropsychological deficits in schizophrenia and current age (Heaton et al, 1994; Mockler et al, 1997), age at onset of illness, or illness duration (Heaton et al, 1994). The authors of these studies claim their results lend support to the hypothesis that the cognitive impairments seen in schizophrenia are of a non-progressive i.e. static nature.

The IQ of the subject will clearly influence their ability to perform certain memory tasks - as discussed above, people with learning disabilities show specific deficits. However, some tasks are more dependent on the pre-existing abilities of the subjects than others. A story recall task may contain words which are unfamiliar to the subject while tests of semantic memory may assume prior knowledge e.g. who is the president of the United States of America.

Some patients may be unco-operative with testing for reasons that are difficult to ascertain. Some patients with predominantly negative symptoms may be unreceptive to testing, or perform poorly due to a lack of motivation or volition to succeed. A minority of studies show no effect of negative symptomatology on memory function (e.g. Dickerson et al, 1991), but an additional confounder to this area is that those subjects who show negative symptomatology are almost invariably taking psychotropic medication.

In a group of antipsychotic naive subjects living in India, McCreadie and colleagues (1997) have shown that poor performance on the Weschler Memory Scale correlates with negative symptoms, as measured by the PANSS. Interestingly, in this study, there were no differences in memory function between these patients and a matched control group of patients with schizophrenia who had been treated with antipsychotic agents. Furthermore, verbal memory deficits have been shown to be present in first episode neuroleptic naive patients with schizophrenia and be relatively independent of both positive and negative symptomatology (Saykin et al, 1994).

The effect of antipsychotic medication on human memory remains unclear. In people with schizophrenia the acute use of antipsychotic drugs seems to improve cognitive function (Baker, 1968), but the effects of long term use remain uncertain (Kirkpatrick et al, 1987). In contrast, it has been shown experimentally that anticholinergic agents impair memory (Frith, 1984) and that ECT causes a temporary impairment of memory (Squire and Chace, 1975). In addition to taking prescribed medication, people with schizophrenia may abuse alcohol and consume illicit substances, both of which may lead to impairment of cognitive function.

## 7.2 Method

The Rivermead Behavioural Memory Test (RBMT) of Wilson et al (1985) was chosen for administration to the 101 subjects in this study. It is designed to give a measure of everyday memory performance and comprises 12 sub-sets. The RBMT has been validated in a population of 176 brain injured adults (mean age 44.4, range 14-69), as well as an age and socio-economic matched population of 118 normal controls (mean age 41.2, range 16-69). The brain damaged patients comprised 60 people with moderate to severe closed head injuries, 76 cerebrovascular accident rehabilitation patients and 40 other patients with variable diagnoses, including cerebral tumours and carbon monoxide poisoning.

The 12 sub-types of the test measure verbal memory (remembering a name), recognition memory for faces (prosopagnosia) and objects, story recall (verbal retrieval memory), remembering a route (procedural learning), measures of orientation and general knowledge and three measures of prospective memory i.e. remembering to do things. Two overall scores may be derived, a screening score (0-12) and a standardised profile score (0-24). The former score indicates whether or not significant memory impairment is present i.e. only 4% of normal controls had a screening score of less than 7. The latter score may be used to allocate subjects to one of four categories (i.e 21-24 normal memory ability, 17-21 poor memory, 10-16 moderate impairment, 0-9 severe impairment).

The RBMT is acceptable to subjects, many enjoy the quiz type format. The test protocol takes approximately 25 minutes to complete. The RBMT for children has been validated in people with Down's syndrome (Wilson and Ivani-Chalian, 1995). The most difficult sub-test for this population was story recall.

The adult version of the RBMT was chosen for administration to the subjects in this study due to; its acceptability, being relatively unaffected by overall level of intelligence, the fact that scores may be broken down into various components, and because it reflects the ability of an individual to function in everyday tasks.

It was not possible for the rater to be blind to diagnosis in this study. Between group differences in total scores were assessed by a one-way ANOVA with a post-hoc least significant differences test. A histogram and cumulative percentage graph of standard profile and screening scores respectively were plotted. Between group differences in individual RBMT item scores were analysed by Kruskal Wallis one-way ANOVA and  $\chi^2$  tests. Correlations with other variables were performed using Spearman's correlation co-efficient. Within group differences as determined by epilepsy, depot medication and anticholinergic medication were examined using an independent sample t-test.

### 7.3 Results of the RBMT

#### 7.3.1 Between group RBMT screening and standardised profile scores



The RBMT was completed by 37 co-morbid subjects, 27 learning disability controls and all 34 schizophrenia controls. Of the three subjects who did not complete the test, two co-morbid subjects were unable to attend for the time required to finish the test and one learning disability subject did not wish to undertake the test.

The results of the screening score and standardised profile score are shown in table fourteen.

Table 14 - RBMT screening scores, standardised profile scores and standardised profile scores with IQ dependent components (date and story recall) subtracted.

<u>GROUP</u>	<u>Screening Score Mean (s.d)</u>  <u>Range (0-12)</u>	<u>Profile Score Mean (s.d)</u>  <u>Range (0-24)</u>	<u>Profile Score (Minus IQ dep.) Mean (s.d)</u>  <u>Range (0-20)</u>
CO – MORBID (N=37)	4.4 (2.3)	10.2 (4.8)	8.2 (3.9)
LEARNING DISABILITY (N=27)	5.4 (3.0)	12.6 (5.3)	10.5 (4.0)
SCHIZOPHRENIA (N=34)	8.4 (2.3)	18.4 (4.0)	14 (3.2)

A one way analysis of variance was performed on each of the above scores. Significant differences between the three groups (at the level of  $p < 0.001$ ) were found between all three scores. A post-hoc least significant difference test was applied to these scores. The results of this are shown in Table 15.

Table 15 - One way ANOVA with post-hoc LSD of RBMT scores between groups

SCORE	GROUP COMPARISONS (Best performance first)	SIGNIFICANCE LEVEL
SCREENING SCORE	L.D. > CO-MORBID	NS
	SCZ > L.D.	$P < 0.001$
	SCZ > CO-MORBID	$P < 0.001$
PROFILE SCORE	L.D. > CO-MORBID	$P = 0.05$
	SCZ > L.D.	$P < 0.001$
	SCZ > CO-MORBID	$P < 0.001$
PROFILE SCORE (MINUS IQ)	L.D. > CO-MORBID	$P < 0.05$
	SCZ > L.D.	$P < 0.001$
	SCZ > CO-MORBID	$P < 0.001$

Figure two illustrates the RBMT standardised profile scores for each of the three subject groups. A left shifted normal distribution is evident when co-

morbid subjects are compared to schizophrenia controls, with learning disability controls spanning both distributions. Figure three illustrates the cumulative percentage of subjects attaining scores on the RBMT screening score. As indicated above only 4% of normal controls scored less than 7 in the validation of the RBMT. This compares to approximately 90% of co-morbid subjects, 75% of learning disability controls and 40% of schizophrenia controls.

### 7.3.2 Between group individual RBMT components.

Using the standardised profile scoring system each of the 12 sub-scales of the RBMT is scored from 0-2. A Kruskal Wallis one-way ANOVA was performed to determine if differences exist between subject groups on individual sub-scales. Significant differences exist between the groups on all sub-scales except picture recall, immediate route recall and delayed route recall where all three groups perform to the same standard.

A Chi-square test was then used between groups to determine the precise characteristics of the inter-group differences. This showed no differences to exist between the co-morbid subjects and the learning disability controls on any of the test sub-scales. However, schizophrenia subjects perform significantly better on all items than both co-morbid subjects and learning disability controls ( $p < 0.05$ ) with the exception of picture recall, immediate route recall and delayed route recall where no between group differences exist.

Figure 2 - Individual RBMT standardised profile scores

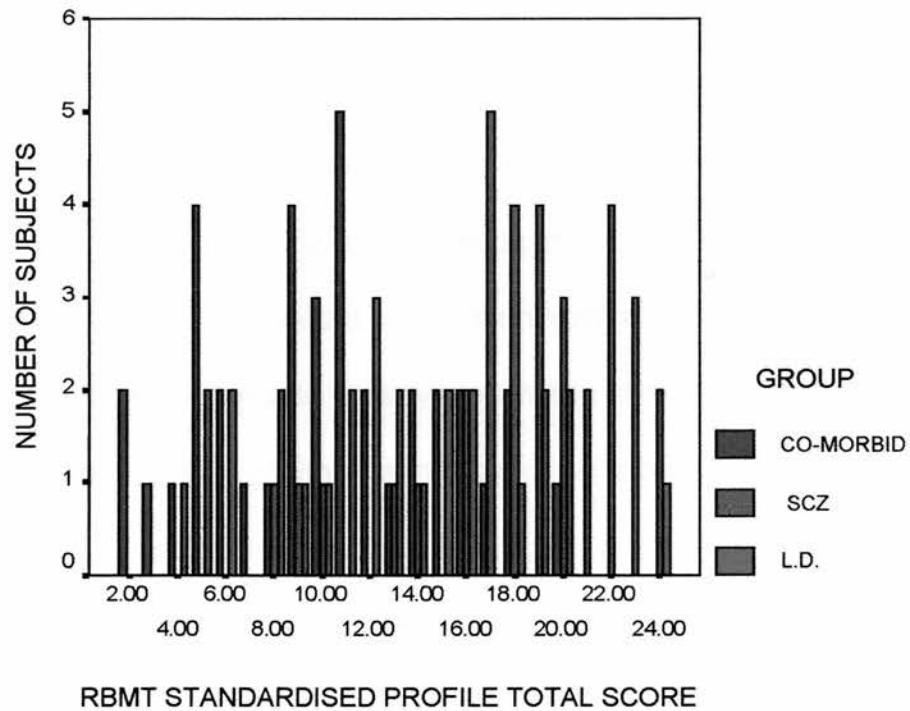
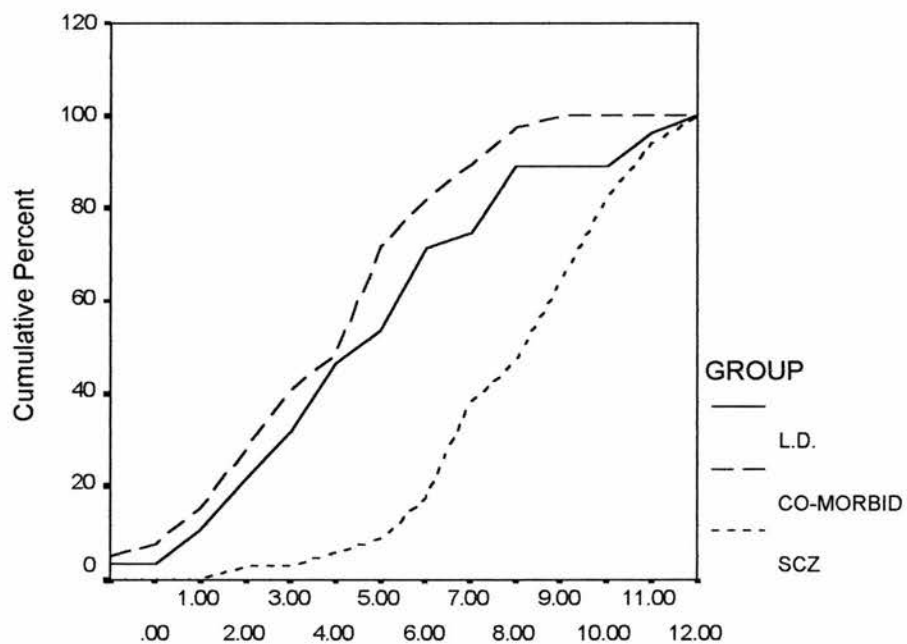


Figure 3 – Cumulative percentage of RBMT screening scores by group



number of offences committed or number of deliberate self harm attempts and RBMT SP scores in any of the groups.

Schizophrenia control subjects show a negative correlation between RBMT SP score and current chlorpromazine equivalent dose of medication (correlation coefficient  $-0.394$ ,  $p=0.021$ ). Hence, the more antipsychotic medication the subject was taking at the time of the study, the more memory impairment is seen. Co-morbid subjects show no correlation between RBMT SP scores and current chlorpromazine equivalent dose of antipsychotic. No subject had received electroconvulsive therapy (ECT) within six months of participating in the study. There was no correlation between the number of ECT treatments given in the past to subjects and current RBMT SP score.

There was a significant negative correlation between the socio-economic group of the subject, as defined by paternal occupation, and RBMT SP score in the schizophrenia control group (correlation coefficient  $-0.348$ ,  $p=0.044$ ), this was not found in either the co-morbid group or learning disability control group.

## 7.4 Discussion

### 7.4.1. Between group differences in memory ability

All three subject groups show impairment of memory, relative to standardised normal controls (Wilson et al, 1985), as determined by the RBMT. Co-morbid subjects and learning disability controls show mean scores consistent with

moderate memory impairment and the mean score of schizophrenia controls is consistent with mild memory impairment. The co-morbid subjects perform significantly worse than either control group. The same results are seen even when the RBMT SP score with 'IQ dependent' variables removed is considered.

The poor performance in co-morbid subjects may at first glance be construed as an additive effect of having both schizophrenia and learning disability, both of which compromise memory function. However, a histogram (Figure 2) of these results shows a clear normal distribution to exist in both subjects with schizophrenia and co-morbid subjects, the latter being shifted to the left. A cumulative percentage graph (Figure 3) shows approximately 90% of co-morbid subjects score less than 7 on the screening score, relative to 75% of the learning disability group. It therefore seems that the memory impairment seen in the co-morbid group is not merely an additive effect, as the distribution seen is similar to the schizophrenia group and does not reflect the broad non-Gaussian pattern of impairment seen in the co-morbid group.

When the sub-scales of the RBMT are considered in greater detail, it is of interest that all three groups perform to the same standard in only three components, picture recall, immediate route recall and delayed route recall. These items test visual recognition memory and procedural memory, respectively. As noted earlier, it is these two types of memory which have been shown by other researchers to remain relatively intact in people with

schizophrenia (Goldberg et al, 1993c). It appears, however, that this is a relatively non-specific finding and that such skills are also relatively intact in people with mild learning disability and no psychoses.

There is another visual recognition task included in the RBMT that involves the identification of non-famous human faces. It is perhaps unsurprising that people with schizophrenia do better on this task than people with learning disability, the task is more correctly considered as a test of prosopagnosia (the inability to recognise faces). Prosopagnosia has been attributed to right hemisphere lesions, specifically of the frontal lobe (Braun et al, 1994) and of the parietal lobe (Young et al, 1992). There is little direct evidence linking the latter right-sided area to the schizophrenia process.

No significant correlations are seen between age and RBMT SP scores in any of the three groups. Furthermore, there are no significant correlations between age of onset of psychosis in terms of symptoms, consultation, admission or diagnosis in either the co-morbid group or the schizophrenia control group. This lends support to the theory that the memory impairment seen in people with schizophrenia is not progressive, but is present from at least the point of diagnosis of the illness, if not before.

#### 7.4.2 The association between the RBMT and IQ scores

All three groups show significant positive correlations between RBMT scores and Quick IQ scores. This further emphasises the difficulty in selecting a

suitable form of memory assessment for the study population and the great inter-dependence of any neuropsychological measure on IQ.

A discussion of the controversial concept of IQ, as defined by psychometric parameters, is beyond the scope of this thesis. However, the existence of a factor of general intelligence, or Spearman's *g*, has been linked to ability for novel problem solving (Duncan et al, 1995). Specifically, in people with frontal lobe lesions, the WAIS-R IQ score is high, but problem solving ability is impaired. It has therefore been suggested that '*g*' may be representative of frontal lobe functions which are independent of WAIS-R derived scores. It is possible therefore, that other IQ independent factors may be associated with structural brain pathology.

Subtle memory impairment may be one of these factors. Hence, memory impairment may not be immediately detected, unless memory function is an integral component of IQ testing. The Quick Test utilises semantic memory encoding and determination of IQ is largely dependent on the size of the acquired lexicon of the individual being tested. Hence, the Quick Test is largely dependent on the ability of the subject to recall the meaning of words in the lexicon - this being something people with schizophrenia find particularly difficult (Goldberg et al, 1993c). It is therefore predictable that, despite attempting to remove the IQ dependent sub-scales, the RBMT scores in the schizophrenia control group correlates positively with the Quick scores.



However, it is perhaps surprising that no such correlation is seen with the co-morbid group if the memory impairment they display is considered to be of a similar nature to the schizophrenia group.

The NART IQ test draws upon visual and verbal recognition memory, thought to be relatively preserved in people with schizophrenia (Goldberg et al, 1993c). This may explain why no association is seen between RBMT SP scores with IQ sub-scales removed and the NART score in the schizophrenia control group, but a positive correlation exists between NART score and RBMT SP score in this group. This finding brings into question the observation that the IQ of people with schizophrenia is seen to vary dependent on whether NART or Quick scores are taken.

It has been argued that the NART provides a measure of pre-morbid IQ and the Quick Test is more a measure of current IQ (Frith et al, 1991). The findings of the present study suggest a mechanism for this observation in people with schizophrenia. i.e. the NART is dependent on visual and verbal recognition recall, as opposed to the Quick Test, which is associated with semantic lexical retrieval. The former is relatively unimpaired in people with schizophrenia, the latter is impaired.

#### 7.4.3 RBMT and clinical variables

The schizophrenia control group shows a negative correlation between socio-economic status and RBMT SP score, which is not replicated in either of the

other two groups. There are no significant correlations between either NART IQ or Quick IQ and social class in the schizophrenia control group. Paternal occupation is known in the majority of schizophrenia control subjects - most derive from the upper three social classes. In the co-morbid and learning disability groups the paternal occupation could not be ascertained in approximately one third of cases, where it is known lower social classes predominate. Hence, there is more information available and the range of social classes is greater in the schizophrenia control group. Nevertheless, the reasons for this association remain unclear.

It has been stated that "IQ scales lack construct validity with psychiatric patients, because defective scores cannot be related to the presumed construct" (Kay, 1988). This alludes to the non-cognitive disorders of schizophrenia that may confound test interpretation e.g. apathy, withdrawal, or lack of attention due to distraction from auditory hallucinations. This statement might apply equally to the assessment of memory function in people with psychotic illness. However, this study has shown no association between symptomatology sub-scales, as determined by the PANSS, and memory scores in any of the three experimental groups. Even though the co-morbid group shows evidence of more negative symptoms than schizophrenia controls, this does not appear to relate to the finding of more episodic memory impairment in this group.

Furthermore, consideration of the relationship between memory scores and clinical variables in the two groups with psychoses e.g. time in hospital, forensic history and deliberate self harm show that no correlations exist. It does not appear that the degree of memory impairment that is present has a direct influence on these variables, or vice versa.

It is of interest that an association is seen between the current chlorpromazine equivalent dose of antipsychotic and memory score in the schizophrenia control group, but not in the co-morbid group. There are no differences between these groups in doses of antipsychotic at the time of the study, or the duration of long term antipsychotic treatment. However, schizophrenia controls who are taking depot medication perform better on memory tests than those who are not receiving parenteral medication. This may be a function of better compliance in this group, i.e. those who receive depot neuroleptics have better compliance with medication regimes than those taking oral antipsychotics and so symptomatology is better controlled. It may be assumed that this effect is not seen in the co-morbid group because they are more likely to live in supported accommodation and therefore the administration of oral medication may be supervised. However, it has already been shown (chapter six) that there are no within group differences in symptom cluster scores in people taking parenteral versus oral medication. It does not therefore appear that this finding is a consequence of inadequate symptom control, due to poor compliance, in people with schizophrenia taking oral antipsychotics.

It has been shown above that high doses of antipsychotic medication are correlated with impaired memory ability in schizophrenia controls. Yet being on depot medication, as opposed to oral, is beneficial to memory functioning in this group, although independent of symptomatology ratings. This seems a paradoxical finding and it is enigmatic that the same results are not seen in the co-morbid group, where no such associations exist, but memory is markedly impaired.

#### 7.4.4. RBMT and epilepsy

Within group RBMT SP scores show that learning disability controls are more impaired if they have a history of epilepsy. This is not replicated in the co-morbid group where no differences exist between RBMT SP scores in those people with a history of epilepsy and those with none.

The co-morbid group are less likely to have experienced a seizure in the last five years and therefore are presumed less likely to be taking large doses of anticonvulsant medications, which may affect cognitive ability. However, when the numbers of people taking anticonvulsant medication at the time of the study are considered in greater detail, only 5 people in each of the co-morbid and learning disability group were actively taking anticonvulsants. There are no significant differences in the RBMT SP scores of these individuals relative to the rest of their group. It does not appear that the differences seen in memory function in people with learning disability and epilepsy are a function of anticonvulsant usage. Similarly, there are no differences in the Quick IQ scores

of people with and without epilepsy in any of the three groups. It appears therefore that people with learning disability alone and epilepsy are more likely to perform poorly on the RBMT than others without epilepsy. This does not appear to be a function of anticonvulsant medication, or IQ per se, and is not replicated in people with co-morbidity and epilepsy. Given that the aetiology of epilepsy is largely idiopathic in both the co-morbid and learning disability groups, it may be that this indicates a different aetiology of the condition between groups.

Gold and colleagues have (1994; 1995) compared memory function in age, and IQ-matched patients with schizophrenia and patients with focal, lateralised temporal lobe epilepsy. People with right temporal lobe epilepsy perform better than those with either left temporal lobe epilepsy or schizophrenia. People with left temporal lobe epilepsy show greater impairment of verbal memory and delayed testing relative to people with schizophrenia. They conclude that a model temporal lobe dysfunction is inadequate to explain the cognitive impairment seen in schizophrenia. The present study did not conduct EEG studies on patients and did not localise epileptic foci.

However, the present study does suggest that perhaps, the occurrence of seizures in the co-morbid group is more intrinsically associated with the occurrence of psychosis than has been previously recognised.

## 7.5. Conclusions

Co-morbid subjects show marked impairment of memory relative to both control groups, as determined by the RBMT. The distribution of impairment is qualitatively similar to that seen in schizophrenia rather than in learning disability, but in quantitative terms is more severe (figure 2).

The findings of relatively intact recognition and procedural memories is not specific to schizophrenia and is also seen in people with mild learning disability alone. There is no correlation with age of onset of schizophrenia and memory impairment in either co-morbid or control group suggesting that memory impairment either commences at the time of onset of the illness or predates it. Memory impairment in people with schizophrenia is non-progressive and is not related to symptom clusters, as determined by the PANSS.

The memory impairment of people with co-morbid mild learning disability and schizophrenia resembles that of people with schizophrenia and a normal pre-morbid IQ, although it is more extreme and not affected by antipsychotic medication. It differs from the memory impairment seen in learning disability alone in terms of its distribution, severity and lack of association with concomitant epilepsy. The severity of the memory deficits seen in the co-morbid group do not appear to be an additive effect of the presence of psychosis and a lowered IQ.

## CHAPTER EIGHT

### NEUROLOGICAL “SOFT” SIGNS IN THE STUDY POPULATION

*“The tendon reflexes are often more or less considerably increased..... skin and mucous membrane reflexes were often weak.”*

Kraepelin, 1919

#### 8.1. Introduction

It has been consistently demonstrated that patients with schizophrenia have more abnormalities on systematic clinical neurological examination than non-psychiatric normal controls (Heinrichs and Buchanan, 1988). These abnormalities tend to be minor and are often termed neurological “soft” signs (NSS). It is generally agreed that NSS are indicative of dysfunction in three discrete areas; integrative sensory functioning, motor co-ordination and the sequencing of motor acts (Schröder et al, 1992). NSS have been documented to occur in up to 98% of people with schizophrenia (Lane et al, 1996) and approximately 5% of normal controls (Schaffer, 1978).

A major difficulty in the interpretation of an excess of NSS in schizophrenia has been the issue of determining whether they represent a trait characteristic of the illness, correlated with pre-morbid asociality and cognitive impairment (Quitkin et al, 1976), or a state dependent characteristic, dependent on drug status (Torrey, 1980), negative psychopathology (Merriam et al, 1990), or non-specific factors, such as attention and concentration (Nasrallah et al, 1982).

The interpretation of an excess of NSS in schizophrenia has been further complicated by the diversity of scales used by researchers (e.g. Manschreck and Ames, 1984; Buchanan and Heinrichs, 1988; Merriam et al, 1990;

Schröder et al, 1992; Flashman et al, 1996). Some studies have simply referred to a “standard neurological evaluation” being performed to rate NSS (e.g. Kinney et al, 1986).

There are four main types of study in this area, those with no control groups, those with normal control groups, those with other psychiatric control groups and those involving first degree relatives of people with schizophrenia.

Barnes and colleagues (1995) assessed 48 people with schizophrenia for primitive reflexes and found 58% to have at least one and 23% at least two, no control group was used. Others studies without control groups (Kolakowska et al, 1985; Merriam et al, 1990; Flashman et al, 1996; King et al, 1991; Chen et al, 1996; Lane et al, 1996; Wong et al, 1997; Malla et al, 1997) have focused on the correlates of NSS in schizophrenia with other variables.

An association between NSS and positive symptoms has been demonstrated (King et al, 1991; Schröder et al, 1992), and also an association with NSS and negative symptoms (Merriam et al, 1990; King et al, 1991; Wong et al, 1997). Other studies show no such associations to be present between NSS and psychopathology (Kolakowska et al, 1985; Chen et al, 1996; Malla et al, 1997). Cognitive impairment has been linked to an excess of NSS in schizophrenia in two studies without control groups (i.e. Kolakowska et al, 1985; Wong et al, 1997) and in one study which included a group of normal controls (Taylor and Abrams, 1984).



Other studies which compare people with schizophrenia with normal controls (Schröder et al, 1992; Gupta et al, 1995;) all show people with schizophrenia to have significantly more NSS than controls. The second study also found an excess of NSS in subjects with schizophrenia who were neuroleptic-naive.

Other investigators have compared people with schizophrenia with other psychiatric populations (Cox and Ludwig, 1979 (five groups); Manschreck and Ames, 1984 (affective patients and normal controls); Mohr et al, 1996 (alcohol dependent patients)). These studies show people with schizophrenia have more NSS than other psychiatric patients, except alcohol dependent patients. The number of NSS correlates with the width of the third ventricle (Mohr et al, 1996) in people with alcohol dependency and both positive and negative symptomatology in people with schizophrenia.

In the last category are those studies which compare subjects with schizophrenia to their own well first degree relatives, and normal controls (Kinney et al, 1986; Rossi et al, 1990; Cantor-Graae et al, 1994a (discordant monozygotic twins); Ismail et al, 1998). All studies show that both schizophrenia subjects and their well relatives have an excess of NSS compared to normal controls. A discordant monozygotic twin study (Cantor-Graae et al, 1994a) provides evidence linking the presence of NSS to obstetric complications in the unaffected co-twin.

## 8.2. Method

The Neurological Evaluation Scale (NES) is a structured instrument for the evaluation of neurological signs in schizophrenia (Buchanan and Heinrichs, 1989). It consists of 26 discrete items, 14 of these are lateralised to left and right sides of the body. It includes items from three areas of functional interest i.e. integrative sensory dysfunction (extinction, agraphaesthesia, astereognosis, right / left confusion, and audio-visual integration), motor inco-ordination (tandem walk, finger to nose, finger to thumb opposition, and dysdiadochokinesis), and sequencing of complex motor acts (the fist-ring, fist-edge-palm, and Ozeretski tests). It also provides an assessment of cerebral dominance, frontal release signs (primitive reflexes i.e. grasp, suck, snout and glabellar reflexes), short-term memory and eye movement abnormalities. Each item is scored on a 0-2 scale, where 0 = no abnormality, 1 = mild, but definite impairment, 2 = marked impairment, primitive reflexes are scored as either present (2) or absent (0). The total protocol takes approximately 25 minutes to complete and is generally acceptable to subjects.

The NES was incorporated into the main study protocol and performed on all subjects in this study (N=101). It was not possible for the rater to be blind to the diagnosis of the subject. Statistical analyses of the results were divided into three main categories, between group differences for total and sub-divided scores (one-way ANOVA with post-hoc least significant difference test), within group differences (independent sample t-test for continuous parametric data) and within group correlations (Pearson correlation co-efficient for parametric data).

## 8.3 Results

### 8.3.1 Between group differences

99 subjects completed the NES protocol. Two subjects in the co-morbid group were unable to perform the tasks required - one was confined to a wheelchair and the other was unable to sustain attention for long enough to complete the protocol. These subjects were omitted from the statistical analyses.

Table 17 shows between group differences in total and sub-component NES scores using a one way ANOVA with a post-hoc least significant difference test. The schizophrenia control group perform better on the NES on total and sub-component scores, excluding primitive reflexes, than either of the other groups. They have fewer frontal release signs (primitive reflexes) than people with co-morbidity, but not people with learning disability alone. There are no significant differences seen between co-morbid and learning disability groups on any of the NES scores.

Table 18 indicates the percentage of subjects scoring above zero on the total score and sub-component scores of the NES and between group comparison using a chi squared test.

### 8.3.2 Within group differences

Each group was sub-divided by gender, history of epilepsy and whether or not individuals were receiving depot medication at the time of assessment.

Table 17 - Between group analysis of total NES and sub-component NES

scores (mean scores :one way ANOVA with post-hoc LSD)

	<u>CO-MORBID GP.</u> N = 37 MEAN                  S.D.  (95% CONFIDENCE)		<u>SCZ. CONTROLS</u> N = 34 MEAN                  S.D.  (95% CONFIDENCE)		<u>L.D. CONTROLS</u> N = 28 MEAN                  S.D.  (95% CONFIDENCE)		<u>ANOVA</u>  F value  p value
<u>TOTAL SCORE</u>	20.8	7.7	8.4**	5.3	18.3	7.7	F = 30.1 p < 0.001
	(18.2 - 23.3)		(6.6 - 10.3)		(15.3 - 21.3)		
<u>SENSORY INTEGRATION.</u>	4.8	3.0	1.39**	1.8	4.3	2.4	F = 17.8 p < 0.001
	(3.7 - 5.8)		(0.77 - 2.0)		(3.7 - 5.8)		
<u>COORDINATION.</u>	5.2	3.1	2.4**	2.5	4.8	3.2	F = 9.1 p < 0.001
	(4.2 - 6.3)		(1.5 - 3.3)		(3.6 - 6.1)		
<u>COMPLEX SEQUENCING.</u>	5.6	1.9	2.6**	2.0	5.1	2.1	F = 22.3 p < 0.001
	(4.6 - 6.2)		(1.9 - 3.2)		(4.2 - 5.9)		
<u>PRIMITIVE REFLEXES</u>	1.5	1.2	0.70*	1.0	1.3	1.8	F = 3.6 p = 0.31
	(0.57 - 2.0)		(1.1 - 2.0)		(0.6 - 2.0)		

One-way ANOVA Post Hoc - least significant difference test (p = 0.05).

\* SIGNIFICANTLY DIFFERENT TO CO-MORBID GROUP

\*\* SIGNIFICANTLY DIFFERENT TO CO-MORBID AND LEARNING DISABILITY GROUP

Table 18 - Between group analysis of total NES and sub-component NES scores (% subjects scoring >0;  $\chi^2$  test)

	<u>CO-MORBID GP.</u> N = 37 % SUBJECTS SCORING >0	<u>SCZ. CONTROLS</u> N = 34 % SUBJECTS SCORING >0	<u>L.D. CONTROLS</u> N = 28 % SUBJECTS SCORING >0	<u><math>\chi^2</math> TEST</u>  d.f. p value
<u>TOTAL SCORE</u>	100%	94.1%	100%	NS
<u>SENSORY INTEGRATION.</u>	92.6%	57.6%	97%	d.f. 2 p < 0.001
<u>CO-ORDINATION</u>	94.3%	73.5%	92.6%	d.f. 2 p = 0.023
<u>COMPLEX SEQUENCING.</u>	97.1%	76.5%	96.4%	d.f. 2 p = 0.007
<u>PRIMITIVE REFLEXES</u>	69.2%	38.2%	53.6%	d.f. 2 p = 0.047

Independent t-tests were performed within groups on the five NES scores, the results are shown in table 19. There are no differences in either co-morbid or learning disability controls in NES scores in people with a history of epilepsy relative to people with no history of epilepsy.

Co-morbid subjects who were taking depot antipsychotic medication at the time of the study had significantly more primitive reflexes (frontal release signs) than those with none. This was not seen in the schizophrenia control group, in fact people in this group taking depot antipsychotic medication at the time of assessment were better at sensory integration tasks than those receiving oral or no antipsychotic medication. Male subjects in the learning disability control group showed significantly more impairment of motor co-ordination than females.

### 8.3.3 Within group correlations

Tables 20 illustrates the within group correlation for the co-morbid group and table 21 illustrates the within group correlations for the learning disability control group. Considering the same variables as shown in table 19 for the schizophrenia control group, there are only two significant Pearson Correlation co-efficients. The first is between the NART score and the sensory integration sub-scale of the NES ( $r = -0.37$ ,  $p = 0.039$ ). The second significant correlation is between total NES score and the general symptom score ( $r = 0.36$ ,  $p = 0.45$ ).

Table 19 - Within group mean differences in NES scores dependent on history of epilepsy, depot medication and gender.  
(Student's independent t-tests)

Independent sample t-tests	<u>EPILEPSY</u>			<u>CURRENTLY ON DEPOT</u>			<u>GENDER</u>		
	<u>YES</u>		<u>NO</u>	<u>YES</u>		<u>NO</u>	<u>MALE</u>		<u>FEMALE</u>
	Mean (s.d.)		Mean (s.d.)	Mean (s.d.)		Mean (s.d.)	Mean (s.d.)		Mean (s.d.)
		p value			p value			p value	
<u>TOTAL NES SCORE</u>									
CO-MORBID	21.5 (7.5)	NS	20.2 (7.9)	20.3 (7.6)	NS	21.5 (8.0)	20.0 (6.1)	NS	21.7 (9.3)
SCZ		NA		7.8 (4.8)	NS	9.5 (6.1)	8.3 (5.1)	NS	8.7 (5.8)
L.D.	18.6 (8.0)	NS	17.2 (6.9)		NA		20.6 (8.2)	NS	15.3 (6.0)
<u>SENSORY INTEGRATION</u>									
CO-MORBID	5.0 (2.7)	NS	4.6 (3.3)	4.4 (3.1)	NS	5.4 (2.8)	4.5 (2.3)	NS	5.1 (3.6)
SCZ		NA		0.75 (1.1)	(p=0.003)	2.4 (2.2)	1.3 (1.9)	NS	1.5 (1.6)
L.D.	3.7 (1.7)	NS	4.2 (2.5)		NA		4.3 (2.5)	NS	4.2 (2.4)
<u>MOTOR CO-ORDINATION</u>									
CO-MORBID	5.5 (3.4)	NS	5.1 (2.9)	4.6 (2.9)	NS	6.4 (3.1)	4.9 (2.9)	NS	5.6 (3.2)
SCZ		NA		2.2 (2.2)	NS	2.7 (3.1)	2.6 (2.5)	NS	2.1 (2.6)
L.D.	5.0 (2.9)	NS	4.5 (3.2)		NA		6.1 (3.2)	(p = 0.01)	3.0 (2.2)
<u>COMPLEX SEQUENCING</u>									
CO-MORBID	5.6 (2.4)	NS	5.5 (1.4)	5.7 (2.0)	NS	5.3 (1.7)	5.4 (2.1)	NS	5.7 (1.6)
SCZ		NA		2.8 (2.1)	NS	2.2 (1.8)	2.5 (2.0)	NS	2.7 (1.8)
L.D.	4.3 (1.8)	NS	5.4 (2.3)		NA		5.6 (2.0)	NS	4.4 (2.2)
<u>PRIMITIVE REFLEXES</u>									
CO-MORBID	1.8 (1.1)	NS	1.4 (1.4)	2.0 (1.2)	(p = 0.003)	0.79 (1.1)	1.6 (1.4)	NS	1.5 (1.2)
SCZ		NA		0.71 (1.1)	NS	0.62 (0.96)	0.6 (0.83)	NS	0.7 (1.3)
L.D.	1.5 (1.8)	NS	0.8 (1.0)		NA		1.6 (2.1)	NS	0.8 (1.1)

Table 20 - Co-morbid subjects Pearson correlation co-efficients of NES scores and age of first admission, psychopathology, IQ, memory and CPZ equivalent.

	TOTAL NES	PRIMITIVE REFLEXES	MOTOR COORDINATION	SENSORY INTEGRATION	COMPLEX SEQUENCING
AGE AT ADMISSION					
POSITIVE SYMPTOMS					
NEGATIVE SYMPTOMS					
GENERAL SYMPTOMS					
NART					
QUICK					-0.36 (p=0.035)
RBMT SP SCORE	-0.50 (p=0.001)		-0.40 (p=0.016)		
CPZ EQUIVALENT					
DEPOT DURATION		0.44 (p=0.006)			

Table 21 - Learning disability control subjects Pearson correlation co-efficients of NES scores and age of first admission, psychopathology, IQ, memory and CPZ equivalent.

	TOTAL NES	PRIMITIVE REFLEXES	MOTOR CO-ORDINATION	SENSORY INTEGRATION	COMPLEX SEQUENCING
AGE AT ADMISSION		0.046 (p=0.013)			
POSITIVE SYMPTOMS					
NEGATIVE SYMPTOMS	0.47 (p=0.22)	0.46 (p=0.025)	0.42 (p=0.046)	0.50 (p=0.016)	
GENERAL SYMPTOMS					
NART					
QUICK					
RBMT SP SCORE					
CPZ EQUIVALENT					
DEPOT DURATION					



## 8.4 Discussion

### 8.4.1 Frequency of NSS

This study is the first to consider the occurrence of soft neurological signs in people with both schizophrenia and mild pre-morbid learning disability. It is also the first to compare a group of people with schizophrenia to two age and sex-matched groups who demonstrate more NSS than people with schizophrenia.

94.1% of subjects with schizophrenia display at least one NSS. All subjects with learning disability and co-morbidity have at least one NSS (Table 18). Other studies vary widely in the number of people with schizophrenia who are found to have at least one NSS e.g. 98% (Lane et al, 1996); 92% (Manschreck and Ames, 1984); 46% (Gupta et al, 1995); 37% (Flashman et al, 1996); 23% if never medicated (Gupta et al, 1995). The latter study suggests that NSS in schizophrenia is not simply a medication effect. This is substantiated by the current study that shows NSS to be present in 100% of antipsychotic naive subjects with learning disability and 100% of people with co-morbidity.

The distribution of scores for all four sub-categories of the NES by, subject group are shown in figures 4-7.

### 8.4.2 Motor co-ordination and complex sequencing

People with schizophrenia alone have significantly fewer NSS on three sub-components of the NES than people with learning disability or subjects with co-

Figure 4 - Sensory integration score by group

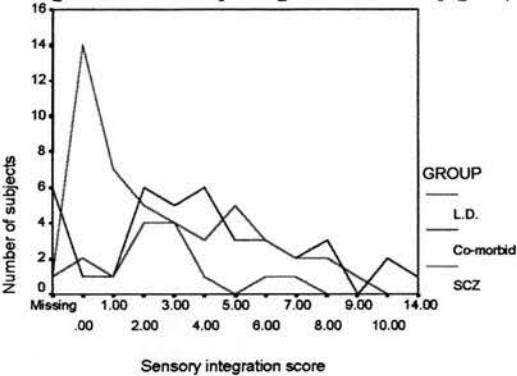


Figure 5 - Motor inco-ordination scores by group

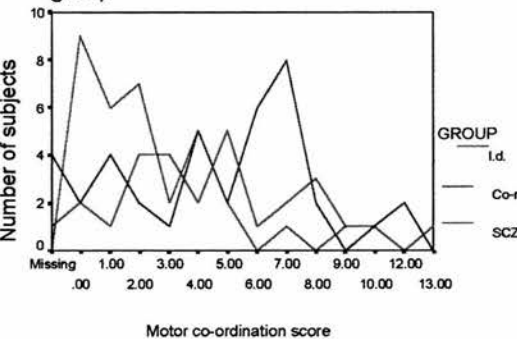


Figure 6 - Complex Motor Sequencing by group

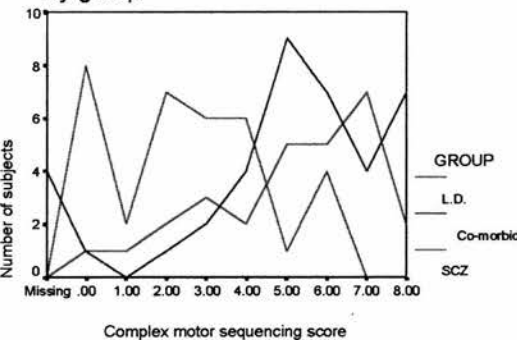
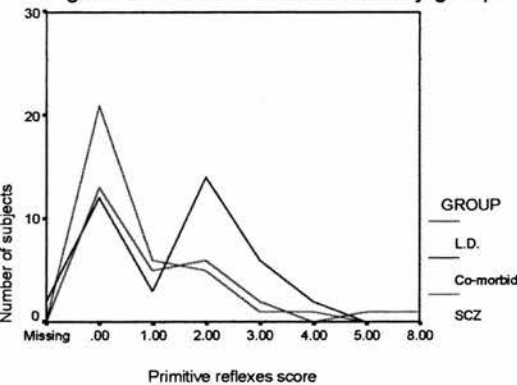


Figure 7 - Primitive reflex scores by group



morbidity. Over 70% of people with schizophrenia show impaired co-ordination ability and complex motor sequencing ability. These sub-scores do not correlate with the amount of antipsychotic medication (chlorpromazine equivalent) taken at the time of participation. Schizophrenia subjects receiving depot preparations do not score any differently to those taking oral medication on these two sub-scales (table 19).

A significant gender effect is seen on mean motor co-ordination scores in the learning disability group. Males have higher mean scores than females, this effect is not replicated in either the schizophrenia or co-morbid group. It is known that some neurodevelopmental disorders are commoner in males than in females e.g. dyslexia, autism, stuttering, Asperger's syndrome (Castle and Murray, 1991). Some neurodevelopmental sex-linked disorders also manifest gender specific phenotypes e.g. fragile X syndrome.

Samples in this study are sex-matched. It may be that some neurodevelopmental disorders remain undescribed in this population either because diagnosis was not sought e.g. fragile X, already known to be associated with motor inco-ordination (Vieregge and Froster-Iskenius, 1989), or because they are hitherto unidentified. Therefore some disorders, which are commoner in men, may have preferentially been chosen as equal numbers of males and females are under study. The nature of these disorders may be such that motor inco-ordination is an intrinsic feature of their presentation.

Motor co-ordination scores and total NES scores negatively co-vary with RBMT SP scores in co-morbid subjects, but no other group. The reasons for this are unclear. Perhaps the NES and RBMT, when assessed together in the co-morbid group, provide an estimation of some form of impairment which is specific to the co-morbid state. Motor co-ordination impairment may also be a correlate of this. No correlations between total NES (or constituent sub-scales) and RBMT SP score are seen in the schizophrenia or learning disability groups. The total NES score does not correlate with the Quick score of the co-morbid group (although the RBMT SP score does) and so this effect does not appear to be explicable by a generalised IQ deficit. This is confirmed as a partial correlation of total NES and RBMT SP scores in the co-morbid group, controlling for the effects of IQ, continues to show a significant negative correlation of -0.471 ( $p = 0.004$ ).

#### 8.4.3 Sensory integration

57.6% of people with schizophrenia have evidence of sensory integration impairment relative to over 90% of subjects in both other groups. These distribution differences between groups are illustrated by figure 4. In this graph the first peak represents those subjects who score 0.

Four items in the sensory integration category (all except audio-visual integration) are traditionally associated with parietal lobe function. There is little direct evidence to support the direct involvement of this area of the brain in

schizophrenia. Relative sparing of these abilities in people with schizophrenia, and a pre-morbid IQ within the normal range, is therefore expected.

3 of the 5 items that comprise this sub-component require the subject to convert information presented in one sensory modality into another e.g. agraphaesthesia, astereognosis, audio-visual integration. It has been discussed, in the context of memory ability (chapter seven), that such a task is particularly difficult for people with lowered IQ. This concept is supported by the significant negative correlation (-0.037) seen between the NART score and the sensory integration score in people with schizophrenia. This may explain why the schizophrenia group perform this task much better than the other two groups, in which subjects are pre-morbidly cognitively impaired.

It is perhaps surprising that people with schizophrenia who are taking depot antipsychotics perform better on sensory integration tasks (figure 19) than those receiving oral preparations.

Neither complex sequencing tasks, motor co-ordination or primitive reflexes are correlated with symptomatology, as rated by the PANSS, in any subject group. Sensory integration ability in people with schizophrenia does correlate positively with general symptomatology. This suggests that performance on this sub-scale may be particularly susceptible to state factors such as anxiety and poor concentration. These state related factors may be modifiable by antipsychotic medication in some people with schizophrenia.

Alternatively, the effect of antipsychotic medication may be to improve the ability of the subject to encode sensory, visual or auditory information into a different form. This effect is not replicated in the co-morbid group, as the reduced baseline IQ in this group continues to make the re-encoding task technically difficult, irrespective of the beneficial effect on concentration which may be conferred by medication. In people with schizophrenia taking depot medication compliance is assumed, relative to those on oral preparations. This may be the reason why people on depot medication are able to perform the tasks more successfully than people on oral preparations in the schizophrenia group.

No differences are seen between people with schizophrenia taking depot or oral medications, in any of the other three NES sub-components. There are therefore two hypothesised mechanisms by which antipsychotic medication improves sensory integration performance in people with schizophrenia and a normal pre-morbid IQ. The first is to minimise state dependent factors which impair performance such as anxiety and poor concentration and the second is to improve the ability of the individual to re-encode information from one sensory modality to another

#### 8.4.4. Primitive reflexes

Primitive reflexes are present during normal fetal and neonatal development, but are not generally present in healthy adults (Humphrey, 1964). They may be

found in patients with specific frontal lobe lesions but are also believed to reflect generalised cerebral dysfunction (Tweedy et al, 1982).

Figure 7 shows the distribution frequencies of primitive reflexes between the three groups. A clear bi-modal distribution occurs in all three groups. This represents those with primitive reflexes and those with none. This is the lowest scoring sub-component of the NES for all groups. 38.2% of people with schizophrenia and 69.2% of co-morbid subjects have evidence of primitive reflexes, these differences are statistically significant. Prevalence figures of primitive reflexes in other studies of schizophrenia are variable e.g. 58% (Barnes et al, 1995); 55% (Keshavan et al, 1979); 52% (Youseff and Waddington, 1988a).

It is of interest that subjects with schizophrenia score no differently to learning disability subjects on this variable, but that co-morbid subjects score significantly higher than either other group. This effect is especially seen in those co-morbid subjects receiving depot antipsychotic medication (figure 19). Such a result is unlikely to be spurious as there is also a significant positive correlation between the time the subject has been receiving depot medication and the number of primitive reflexes seen, which occurs in the co-morbid group only.

One of the primitive reflexes examined in the NES is the glabellar tap. This may be a manifestation of drug-induced parkinsonism. The findings of this

study therefore suggest that co-morbid subjects are more susceptible to the development of antipsychotic induced Parkinsonism, especially when taking depot preparations, than people with schizophrenia alone. This may also be the reason why co-morbid subjects score higher than the antipsychotic naive learning disability group on this sub-category of the NES alone. The prevalence of spontaneous involuntary movements in the study population will be considered further in chapter ten.

The learning disability group are assumed to have generalised cerebral dysfunction producing primitive reflexes. Although people with schizophrenia alone demonstrate primitive reflexes to the same degree as the learning disability group, the aetiology may be different and concern frontal lobe abnormality which has been associated with the disease (e.g. Andreasen et al, 1986; Weinberger, 1988) rather than diffuse brain changes per se.

#### 8.4.5 Psychopathology and IQ

The only correlation with PANSS rated symptomatology and NES scores in people with schizophrenia, or co-morbidity, is a positive correlation with general symptomatology and sensory integration in schizophrenia. This is presumed to relate to state, rather than trait characteristics, as described above. This study has found no relationship between positive or negative symptoms and NSS in people with schizophrenia or co-morbidity.



In contrast, significant positive correlations with negative symptoms were found in all NES scores, except complex sequencing, in people with learning disability alone. The reasons for this are unclear. The learning disability group have a restricted range of all psychopathology items scoring significantly less than the other groups. This result may relate to a floor effect of this variable.

Alternatively, the correlation may be specifically associated with the negative symptom variable, "difficulty in abstract thinking" on which 12 people with learning disability score more than 0 (range 0-4). This is the only variable to have a mean score within the clinically significant range for negative symptomatology in the learning disabled group.

In terms of IQ there are no correlations between total NES scores and IQ as measured by the Quick in any group. There are two negative correlations seen with sub-component scores of the NES, complex sequencing and Quick in the co-morbid group, and sensory integration and NART in the schizophrenia group, as discussed above.

## 8.5 Conclusions

98 of the 99 subjects in this study had at least one NSS, as rated by the NES. People with schizophrenia have fewer NSS in all sub-categories than co-morbid subjects, who have the same amount of NSS as people with mild learning disability in all categories, except primitive reflexes. Therefore NSS

are non-specific and mean scores are higher in people with learning disability than people with schizophrenia alone.

There are no within group effects of gender or epilepsy, in either the schizophrenia or co-morbid groups. Similarly, the total NES scores in these groups are not associated with antipsychotic medication, psychopathology or IQ scores. It appears that the total NES score is a trait, as opposed to state, measure in these two groups. Given that negative correlations are seen with negative symptoms, specifically difficulty in abstract thinking, in people with learning disability alone, NSS may be more dependent on state, rather than trait, factors in this group.

Two NES sub-components are noteworthy. Firstly, the sensory integration score which relates to an IQ dependent processing mechanism and may be trait dependent in people with schizophrenia alone. Performance on this sub-scale may be improved by antipsychotic depot medication in people with schizophrenia.

Secondly, primitive reflexes occur in people with schizophrenia to the same extent as antipsychotic-naive people with learning disability alone. More primitive reflexes are seen in co-morbid subjects. This may be a consequence of an increased susceptibility to the Parkinsonian side effects of antipsychotic medication, scores are increased by depot medication, or an aetiological

combination of both diffuse cerebral dysfunction and frontal abnormalities in the co-morbid group.

Finally, an important positive correlation exists between total NES score and RBMT SP score in the co-morbid group. The co-morbid group perform worse than both control groups on the RBMT and worse than the schizophrenia group on all NES scores. If a specific syndrome is associated with co-morbidity then the deficits produced may be what is being specifically measured by the RBMT and NES with greater construct validity than the schizophrenia control group. No such correlation between these scores exists in people with schizophrenia and a normal pre-morbid IQ. Furthermore, this relationship does not appear to be explicable in terms of IQ deficits. It is not seen in the learning disability control group and only one sub-component of the NES (complex sequencing) correlates with Quick IQ in the co-morbid group.

Although NSS are non-specific findings they seem to be state dependent in people with schizophrenia and trait dependent in people with learning disability. In people with co-morbidity the relationship between NES total score and RBMT SP score and also the occurrence of primitive reflexes appear to be of importance when attempting to characterise the discrete nature of schizophrenia as it occurs in this population.

## CHAPTER NINE

### MINOR PHYSICAL ANOMALIES IN THE STUDY POPULATION

*“all sorts of physical abnormalities exist with striking frequency, especially weakness, small stature, youthful appearance, malformation of the cranium and of the ears, high and narrow palate, persistence of the intermaxillary bone, abnormal growth of hair, strabismus, deformities of the fingers or toes, polymastia, defective development and irregularity of the teeth and the like.”*

*Kraepelin, 1919*

#### 9.1 Introduction

Minor physical anomalies (MPAs) are externally visible physical characteristics, of no serious medical or cosmetic consequences, that are believed to be associated with developmental processes occurring during the first trimester in utero. As the central nervous tissue derives from ectodermal cells, it is believed that the presence of excess MPAs may relate to concomitant neurodevelopmental abnormalities. (Guy et al, 1983). More recently Green and colleagues (1994a) have suggested that MPAs may be associated more with second trimester maldevelopment than first trimester. This derives from work finding an association between MPAs and dermatoglyphic asymmetry (Green et al, 1994a).

The standard instrument for the assessment of MPAs, was developed by Waldrop and colleagues, principally for use in children with Down's syndrome or hyperactivity (Waldrop et al, 1968; Waldrop and Haverson, 1971). Subsequently, an increased number of MPAs were found in other childhood conditions e.g. autism (Rapoport et al, 1974) learning disability (Steg and Rapoport, 1975) and psychosis (Campbell et al, 1978).

Table 22 - Studies since 1982 of Minor Physical Anomalies (MPAs) in Schizophrenia.

<u>AUTHORS</u>	<u>SUBJECT GROUPS</u> (NUMBER OF SUBJECTS)	<u>MAIN FINDINGS</u>
Gaulteri et al, 1982	Schizophrenia (64) Alcohol dependency (38) Normal controls (95)	Increased MPAs in schizophrenia. Bimodal distribution in alcohol dependency.
Guy et al, 1983	Schizophrenia (40) (all male)	Increased MPAs in schizophrenia. MPAs correlate with poor pre-morbid adjustment and low current IQ.
Lal & Sharma, 1987	Schizophrenia (80) Normal relatives (80)	Increased MPAs in schizophrenia compared to normal relatives.
Green et al, 1987	Schizophrenia (early onset < 18yrs (20)) (middle onset 19-21(16)) (late onset > 22 (14))	Increased MPAs in early onset schizophrenia relative to middle and late onset.
Green et al, 1989	Schizophrenia (67) Normal controls (88)	Increased MPAs in schizophrenia, esp. early onset, excess of mouth signs. Increased head circumference in females.
Nizamie et al, 1989	Schizophrenia (Acute - 47) (chronic - 60)	Increased MPAs in chronic schizophrenia relative to acute.
O'Callaghan et al, 1991	Schizophrenia (41)	MPAs are associated with FH of schizophrenia (esp. mouth), maternal obstetric complications and being male
Lohr & Flynn, 1993	Schizophrenia (118) Affective disorder (33) Normal controls (31)	Increased MPAs in schizophrenia only, more if tardive dyskinesia present. No associations with symptoms or socio-economic group.
Green et al, 1994b	Schizophrenia (63) + well siblings (33) Bipolar (manic) (26) + well siblings (9) Normal controls (40)	Increased MPAs in schizophrenia only. Bipolar MPAs same as controls and both sibling groups.

<u>AUTHORS</u>	<u>SUBJECT GROUPS</u> (NUMBER OF SUBJECTS)	<u>MAIN FINDINGS</u>
Cantor-Graae et al, 1994	Discordant monozygotic twins - schizophrenia (22) Concordant MZ twins - schizophrenia (11) Normal MZ twins (6)	<u>NO</u> increase in MPAs in any of the three groups. Complications of early pregnancy associated with MPAs in all groups
Alexander et al, 1994	Schizophrenia (41) Bipolar (8) Learning disability (19) Normal controls (14)	Increased MPAs in learning disability group. <u>NO</u> increase in MPAs in schizophrenia (trend only relative to normal controls)
Waddington et al, 1994	Schizophrenia (47)	Orofacial tardive dyskinesia associated with MPAs of the head i.e. cranio-facial dysmorphogenesis
McGrath et al, 1995	Schizophrenia (79) Schizoaffective (31) Mania (24) Major Depression (13) Unspecified functional psychosis (8) Organic psychosis (2) Normal Controls	All ill subjects had increased MPAs relative to controls. MPAs not specific to any diagnosis. Anomalies of palate commonest in both ill subjects and controls. No associations with age of onset, symptoms, Pre-morbid IQ, current IQ or obstetric complications.
Lohr et al, 1997	Schizophrenia early onset (<45 yrs - N=15) Schizophrenia late onset (> 45yrs - N=8) Alzheimer's disease (11) Unipolar depression (11) Normal controls (15)	Increased MPAs in early and late onset schizophrenia and unipolar depression relative to normal controls. <u>NO</u> increased MPAs in Alzheimer's disease
Griffiths et al, 1998	Familial schizophrenia (32) Well 1st degree relatives from multiply affected families (63) Sporadic schizophrenia (28) Well 1st degree relatives of sporadic schizophrenia (44) Normal controls (47)	Increased MPAs in schizophrenia only when broad criteria used. More MPAs in sporadic rather than familial schizophrenia, esp. males. No increased MPAs in familial schizophrenia or either groups of 1st degree relatives.

The first study to find an excess of MPAs in adults with schizophrenia (Gaultieri et al, 1982) utilised a normal control group and group of subjects with alcohol dependency. This study showed an excess of MPAs in the group of people with schizophrenia relative to both the normal control group and the group of people with alcohol dependency. It was noted that the latter group displayed a bimodal distribution of MPA's. Subsequent studies then began to focus on the finding of excess MPA's in schizophrenia and these are shown in table 22.

Greene and colleagues (1989) replicated and elaborated the results of Gaultieri and colleagues (1982), demonstrating an excess of MPAs in schizophrenia compared to normal controls, especially those involving the mouth. MPAs also seemed to be more common in early onset cases of schizophrenia (Green et al, 1989). Other investigators have attempted to find clinical correlates of MPAs in groups of people with schizophrenia (Guy et al, 1983; Green et al, 1987; Nizamie et al, 1989; O'Callaghan et al, 1991 and Waddington et al, 1994). Correlations have been found with poor pre-morbid adjustment and current IQ, early onset, duration of illness, family history of schizophrenia, and orofacial dyskinesia respectively.

The specificity of MPAs to schizophrenia have been considered by several authors (Lohr and Flynn, 1993; Green et al, 1994b; Alexander et al, 1994; McGrath et al, 1995 and Lohr et al, 1997) All of these studies included people with affective disorders as controls. Two studies found an increased number of MPAs in affective subjects (McGrath et al, 1995 (unipolar and manic); Lohr et



al, 1997 (elderly unipolar)) and the remaining three studies did not. Interestingly McGrath reported that the commonest type of MPA in both normal controls and people with functional psychoses are palatal abnormalities. In the first attempt to conduct a blind to diagnosis Waldrop scale examination, Alexander and co-workers found an increase in MPAs in males with learning disability, but not people with schizophrenia compared to normal controls. However, the degree of learning disability which these subjects had was not specified, nor was the presumed aetiology of their cognitive impairment.

Several recent studies have considered the familial aspects of MPAs by comparison of the well relatives of people with schizophrenia to probands (Green et al, 1994b; Cantor-Graae et al, 1994; Griffiths et al, 1998). The results of all three studies are quite disparate. The first study (Green et al, 1994b) found no excess of MPAs in the siblings of people with schizophrenia. The second study (Cantor-Graae et al, 1994) considered monozygotic twins, both concordant and discordant for schizophrenia, in addition to normal twins. No excess of MPAs were found in any of their three groups, however in all groups a correlation was found between MPAs and early pregnancy complications. Finally, the Maudsley family study (Griffiths et al, 1998) provides evidence for an excess of MPAs to be seen in males with schizophrenia and no family history of the illness. This study concurs with the work of Lal and Sharma (1987) and Green et al (1994b), with no excess of MPAs being found in relatives.



In summary, MPAs are not specific to schizophrenia. Historically, they were first noted to occur in children with autism and hyperactivity, subsequently an excess was noted in people with affective disorder, other functional psychoses (McGrath et al, 1994) and males with learning disability (Alexander et al, 1994). It has been suggested that MPAs are more commonly associated with schizophrenia of early onset (Green et al, 1987; Green et al, 1989; Lohr et al, 1997), although this finding is not consistent (McGrath et al, 1994). Others have found associations with MPAs specifically in males with schizophrenia (O'Callaghan et al, 1991; Griffiths et al, 1998), those with a positive family history of schizophrenia (O'Callaghan et al, 1991) or sporadic cases with no family history (Griffiths et al, 1998). Two studies find an association between MPAs and tardive dyskinesia (Lohr and Flynn, 1993; Waddington et al, 1994). Others workers have suggested that MPAs are linked with early pregnancy complications (Cantor-Graae et al, 1994; O'Callaghan et al, 1991), although evidence to the contrary is also available (McGrath et al, 1995).

No previous study has assessed MPAs in people with schizophrenia and a pre-morbid IQ in the mildly learning disabled range.

## 9.2 Method

A five minute physical examination was completed on all subjects (N=101) to enable completion of the Waldrop scale. With the exception of footwear, this did not involve the removal of any clothing and was acceptable to subjects.

The Waldrop scale considers six body regions in detail; the head, eyes, mouth, ears, hands and feet. This study used the modified Waldrop scale of Guy et al (1993). In some studies measurement of head circumference has been omitted due to a lack of normative data e.g. O'Callaghan et al, 1991, or because normative head circumference data in different ethnic groups was not available. In the present study normal head circumference and intercanthal distance for males and females was taken from standardised British developmental tables (Smith, 1976).

The Waldrop scale may be scored in several different ways, both weighted and unweighted total scores were calculated for this study. When weighted scores are calculated a higher score of 2 is given to some items (e.g. fine hair that will not comb down, head circumference >2 standard deviations outwith the normal range, fifth finger markedly curved inward) at the expense of others (e.g. two or more hair whorls, soft and pliable ears, smooth tongue with rough spots) which receive a score of zero. When the unweighted score is calculated each item is given the same value, one if present and zero if absent.

Mean scores were calculated for both weighted and unweighted scores for each of the three groups of subjects and compared using a one-way ANOVA with a post-hoc least significant difference test. The frequencies of individual items were calculated and between group comparisons made using the Kruskal Wallis one-way ANOVA. Groups were sub-divided by gender, epilepsy history, and age of first symptoms (> 18years vs.< 18 years) inter-group

weighted and unweighted mean scores were compared using independent sample t-tests. Finally, Pearson correlations were applied to the data for individual groups to seek associations between age of first symptoms, NART, Quick test, RBMT SP score, total NES score, CPZ equivalent and PANSS determined psychopathology clusters.

9.3. Results

9.3.1. Within group differences

46.2% of the co-morbid group, 42.9% of learning disability controls and 38.2% of people with schizophrenia score 5 or more on the Waldrop unweighted scale. The mean weighted and unweighted Waldrop scores and standard deviations were computed for each group (table 23).

Table 23 – Mean weighted and unweighted Waldrop scores by group.

	CO-MORBID	SCHIZOPHRENIA	LEARNING DISABILITY
MEAN WALDROP WEIGHTED SCORE (S.D.)	4.2 (2.3)	3.9 (2.2)	5.4 (3.0)
MEAN WALDROP UNWEIGHTED SCORE (S.D.)	4.5 (2.5)	4.1 (2.5)	5.5 (3.2)

A one-way ANOVA shows no significant differences to exist between weighted and unweighted Waldrop scores between any of the three groups. A post-hoc least significance difference test indicates that there is a significant difference between people with learning disability and people with schizophrenia for weighted scores only ( $p=0.029$ ). However, when a more discriminatory post-hoc Scheffé Test is performed this significance is lost ( $p=0.090$ ).

The score of individual items of the Waldrop score were considered in descriptive terms. Four items emerged as being the most frequently occurring in all three groups. These were; increased intercanthic distance (64% learning disability, 62% co-morbid; 70.6% schizophrenia), increased distance between second and third toes (29%; 23%; 38% respectively), palatal anomalies (32%; 15%; 24% respectively), and increased head circumference (57%, 56.4%, 53% respectively). There were no significant differences found between any three groups on any of the individual components when item scores were assessed using the Kruskal Wallis one-way ANOVA.

#### 9.2.2. Inter-group differences for gender, epilepsy and age of onset.

There are no significant effects of gender or history of epilepsy on total weighted or unweighted Waldrop scores in any of the three groups (one-way ANOVA).

Co-morbid and schizophrenia subject groups were sub-divided into two dependent on age of onset of first psychotic symptomatology. The two

categories were age of onset greater than 18 years and age of onset less than 18 years, the mean Waldrop scores between these two groups were considered. The co-morbid group show a statistically lower total mean unweighted Waldrop score when schizophrenia symptoms began before 18 years of age (3.4; s.d. 1.5), rather than later (5.2; s.d 2.7; Independent t-test;  $p=0.036$ ).

### 9.3.3 Within group correlations

Pearson correlation co-efficients were derived for the following variables, where relevant, for each group, with both weighted and unweighted Waldrop scores:- chlorpromazine equivalent, NART IQ, Quick IQ, positive, negative and general PANSS symptom clusters, total NES score, RBMT SP score and age at first symptoms of illness.

A positive correlation ( $r = 0.332$ ;  $p=0.048$ ) was found between the weighted Waldrop score and the total NES score in the co-morbid group. A negative correlation ( $r = -0.386$ ;  $p=0.24$ ) was seen between the unweighted Waldrop score and the RBMT SP score in the schizophrenia control group. This group also had significant negative correlations with the Rivermead screening score for both weighted ( $r = -.371$ ;  $p=0.031$ ) and unweighted ( $r = -.448$ ;  $p= 0.008$ ) scores.

## 9.4. Discussion

#### 9.4.1. Methodological issues

The Waldrop scores obtained in this study should be interpreted with caution. There are several inherent methodological issues which are raised by the use of this scale. Firstly, Waldrop scoring, especially the weighting system, was initially designed for use in children with Down's syndrome. Consequently, the weighting score gives priority to items occurring more commonly in people with trisomy 21 (Waldrop et al, 1968). It does not prioritise items on the basis of any other neurodevelopmental criteria and is therefore of little relevance to people with schizophrenia. It is probably more valid to use the unweighted scores in the assessment of subjects without Down's syndrome.

The specificity of the Waldrop score is poor, unless the typical features of trisomy 21 are being sought. This study has emphasised this by failing to find any significant differences between three groups of subjects, who can be clearly differentiated by other parameters e.g. IQ, presence or absence of schizophrenia, memory ability, neurological soft signs. A normal control group was not used in this study and so it cannot be ascertained if there is a relative excess of MPAs in any of the three groups. Reference to the accumulated literature on MPAs is of little assistance in this regard. In four studies where the Waldrop score was used in normal adults (Paulus and Martin, 1986; Green et al, 1989; Lohr and Flynn, 1993; Alexander et al, 1994) there is a wide range of values given for the percentage of subjects who score 5 or more (30%, 3.4%, 0% and 21.4% respectively). Similarly, the percentage of subjects with schizophrenia scoring 5 or more in other studies varies greatly e.g. 90% (Lal

and Sharma, 1987) to 5% (Lohr and Flynn, 1993). In the only study to consider MPAs using the Waldrop scale in people with learning disabilities, the percentage scoring 5 or more was 63.2% (Alexander et al, 1994; all percentage figures were derived from this latter paper). The results of the present study show that all groups appear to have an excess of MPAs, even if it is assumed conservatively that a score of 5 or more is to be expected in 30% of normal people. This emphasises both the poor specificity and sensitivity of the Waldrop.

Further analysis of the sensitivity of the Waldrop scale may lack validity, given that exactly what it seeks to measure in people with schizophrenia and learning disability remains unclear. However, it does seem to indicate that there is a commonality linking the two conditions, which does not appear to be enhanced in the co-morbid state. This is the first parameter to be considered (with the exception of some sociodemographic and clinical variables) to date in this study where no differences exist between the three groups of subjects. It has been suggested that MPAs share genetic and environmental factors with schizophrenia and arise from the same pathogenic substrate, such as a disorder of ectodermal development. (Murphy and Owen, 1996) This approach provides a model linking the association of MPAs in schizophrenia with being male, having a family history and obstetric complications. However as discussed above, and with the possible exception of obstetric complications, even these are not consistently robust findings. There are no differences between male and female MPA scores in any of the three groups in this study.

The second methodological issue to be considered is that the Waldrop scale requires a face to face examination of the subject, given the nature of the examination it would be difficult to perform without any verbal interaction. When studying people with learning disabilities and people with psychiatric illnesses, it may prove impossible to conduct this assessment blind to the subject's diagnosis. It was not practical to consider blind ratings in the present study, as the author conducted the majority of all assessments and had prior knowledge of the diagnoses of all subjects. The one study that has previously compared MPAs in people with learning disability to people with schizophrenia used the Waldrop scale and used two assessors who were blind to diagnosis (Alexander et al, 1994). Unfortunately it is not specified in their paper how this was practically achieved. It has been suggested that photographs of subjects be used (Murphy and Owen, 1996) to obtain blind ratings of MPAs. This would not be possible with the full Waldrop assessment, as head circumference and intercanthal distance need to be measured manually.

#### 9.4.2 The predictive value of MPAs

Given the poor sensitivity and specificity of MPAs in people with schizophrenia the predictive value of their presence in those believed to be at risk of schizophrenia might be also considered to be low. This has been supported by a large study of the offspring of mothers with non-organic psychoses and the offspring of healthy controls (McNeil et al, 1992). No differences in rates of congenital malformations or minor physical aberrations were noted between at



risk subjects and controls at the age of four years. From these results McNeil's group concluded that early developmental anomalies did not represent an expression of genetic influence toward psychosis.

This raises the possibility that the presence of MPA in people with schizophrenia may be related more to environmental factors e.g. obstetric complications, than genetic. The only study to show a clear association between MPAs and a defined environmental event was conducted in Finland (Gaily et al, 1988). 121 children of mothers with epilepsy (study group) were compared to 105 controls born to normal mothers, their mothers and fathers were also examined. All the children were blindly assessed for 80 MPAs at the age of five and a half years. 106 of the study group had been exposed to anticonvulsants in utero and 36% of their mothers had experienced seizures during pregnancy. A significant excess of MPAs were seen in the study group and their epileptic mothers relative to the control group. The excess MPAs were all associated with fetal hydantoin syndrome, which is associated with phenytoin exposure in 7-11% of those at risk i.e. acrofacial features, intellectual deficiency, growth retardation, microcephaly, hypertelorism and digital hypoplasia. However, when children were compared to their mothers it appeared that several of these features were genetically linked to epilepsy and that only hypertelorism and digital hypoplasia were specific to phenytoin exposure. So, although this study links MPAs to a clear environmental event it also demonstrates a genetic association to exist in people with epilepsy.

The present study does not show people with epilepsy, in either the learning disability group or co-morbid group to have an excess of MPAs. This is not surprising as the Waldrop scale only measures one of the items found to be significant in the Finnish study, hypertelorism. This item is the most frequently occurring in all of the three groups. The aetiology of this item is believed to be more environmentally than genetically mediated in the Finnish epilepsy study.

#### 9.4.3 Individual items of the Waldrop scale

Few studies to date have considered in any depth the frequency of occurrence of individual items of the Waldrop scale. Generally this is because the number of subjects in many studies is small and analysis of separate components further reduces the statistical power. In the present study there are no differences between groups in the frequency with which separate Waldrop items occur.

It has been noted that palatal abnormalities and an 'unusual' head circumference, are often seen in people with schizophrenia, (Green et al, 1989), both are these items are relatively common in all groups in this study. The former was first commented upon by Clouston (1883) in descriptions of adolescent insanity at the end of the Nineteenth Century. However, palatal abnormalities are also the commonest type of MPAs seen in normal controls (McGrath et al, 1995).

Head circumferences have been studied independently in neonates born to mothers with schizophrenia and normal neonatal controls (McNeil et al, 1993). When preterm neonates were removed from the analysis, the head circumference of the at risk neonates was noted to be smaller, relative to body length, than controls. It was suggested that small head circumferences at birth may reflect retarded fetal brain growth.

#### 9.4.4.The relationships between MPAs, NSS, the RBMT and IQ.

Another study looking at the offspring of mothers with schizophrenia (Marcus et al, 1985) focused on the relationships between IQ, neurological signs and MPAs. There was a significant relationship between MPAs and neurological functioning, but no relationship between MPAs and IQ. This is consistent with the results of the present study, although a positive correlation is found between MPAs and the NES in the co-morbid group only, no correlations are seen with either the NART or Quick IQ in any of the groups. The RBMT screening score is also noted to correlate negatively with MPAs in the schizophrenia control group.

It is assumed therefore that, like neurological soft signs (NSS), the excess of MPAs seen in the co-morbid group is not a function of a lowered IQ per se, even though an excess of both these parameters also occurs in people with mild learning disability alone. It appears that both NSS and MPAs are more specifically associated with selective environmental and genetic factors than simple IQ recordings. Even though the determination of the IQ of any individual

is ultimately dependent upon both environmental and genetic factors, the mechanism required to produce MPAs and NSS ensures that not every person with MPAs and NSS has a lowered IQ. Hence, it is possible for some people with schizophrenia to have a normal IQ, MPAs and NSS, and others with schizophrenia to have a low pre-morbid IQ, MPAs and NSS.

This is possible as the sequelae of any neurodevelopmental insult is determined by both its timing and its severity (Murphy and Owen, 1996). Hence, MPAs and NSS may result from a small insult in early pregnancy (environmental or genetic) which does not affect overall IQ, but may be sufficient to affect the RBMT score. There is evidence that in early injury re-organisation of the cortex is possible and cognitive sequelae may be minimised (DeVries et al, 1985). Alternatively a large insult at a later stage in development (environmental or genetic) may be so extensive that there is global cerebral damage and IQ is reduced, extensive impairment on the RBMT is then also apparent.

If this theory is correct then obstetric complications of early pregnancy might be associated with schizophrenia with no pre-morbid IQ impairment and those complications of later pregnancy might be associated with schizophrenia with pre-morbid cognitive impairment, MPAs and NSS being evident in both. This is consistent with the available evidence (O'Dwyer, 1997) which states that only five people out of a group of 50 (10%) with co-morbidity had not experienced a complication of pregnancy or birth compared to 13 out of 50 (26%) in a control

group with learning disability and no schizophrenia ( $p = 0.022$ ), groups were matched for epilepsy.

The common factor which was associated with those people with learning disability in O'Dwyer's study who did subsequently develop schizophrenia was birth complications which increase the risk of fetal hypoxia in labour i.e. abnormally long or short labour, maternal pre-eclamptic toxemia, maternal episiotomy. Similarly, the work of Cantor-Graae and her colleagues (1994) indicates that in monozygotic twins who are concordant, discordant and without schizophrenia excess MPAs are present, but are related to early complications of pregnancy in all three groups. None of these subjects are known to have any pre-morbid cognitive impairment.

#### 9.5.Conclusions

Although an excess of MPAs are present in all three subject groups, no group differences are seen in either the frequency of individual items or total Waldrop scores. MPAs are therefore not specific to schizophrenia but are also found in people with mild learning disability. MPAs are unrelated to gender or a history of epilepsy. The predictive value of finding an excess MPAs in people at risk of schizophrenia, particularly when using the Waldrop scale, is probably low.

In people with schizophrenia alone there is no relationship between MPAs and age of onset. In the co-morbid group people who develop the symptoms of

schizophrenia before 18 years of age have significantly fewer MPAs than those who develop schizophrenia later. This is intriguing as no other study has made such an observation in people with schizophrenia and no pre-morbid cognitive impairment, indeed the reverse has been shown to be the case and MPAs have been associated with a earlier age of onset when a normal pre-morbid IQ is present.

Co-morbid subjects have no more MPAs than people with either learning disability alone or people with schizophrenia alone. However, MPAs positively correlate with NSS in the co-morbid group and people with an early onset are likely to have fewer MPAs. It has been suggested that MPAs may result from either genetic or environmental effects during fetal neurodevelopment. Small early insults producing MPAs with relative preservation of IQ and large late insults e.g. fetal hypoxia at birth, producing MPAs with global impairment of IQ and possibly also an excess of NSS. This mechanism may operate in all three experimental groups with a variety of insults at different times of neurodevelopment creating different clinical outcomes.

## CHAPTER TEN

### INVOLUNTARY DISORDERS OF MOVEMENT IN THE STUDY POPULATION

*“The spasmodic phenomena in the musculature of the face and speech, which often appear, are extremely peculiar disorders. Some of them resemble movements of expression, wrinkling of the forehead, distortion of the corners of the mouth, irregular movements of the tongue and lips, twisting of the eyes.....”*

Kraepelin, 1919

#### 10.1 Introduction

##### 10.1.1. Antipsychotic-induced involuntary disorders of movement in people with learning disability.

There have been several studies which consider the specific effect of antipsychotic medication on abnormal movements in people with learning disabilities (Richardson et al, 1986; Murti Rao et al, 1987; Youseff and Waddington, 1988b; Murti Rao et al, 1989; Ganesh et al, 1989; Cohen et al, 1991; Sandev, 1992; Farren and Dinan, 1994; Bodfish et al, 1996). Five of these studies utilised control groups of people with learning disabilities not taking antipsychotic medication (Murti Rao et al, 1987; Murti Rao et al, 1989; Youseff and Waddington, 1988b; Sandev, 1992 (only 6 subjects in control group); Farren and Dinan, 1994). One used a comparison group of people with schizophrenia and a normal pre-morbid IQ who were taking antipsychotics (Cohen et al, 1991).

Richardson et al (1986) examined 299 people in a hospital for people with learning disabilities who had received antipsychotics in the previous year and found that 30% had evidence of tardive dyskinesia. Youseff and Waddington

(1988b) found dyskinesia in 26% of 42 subjects taking antipsychotics, but also in 29% of antipsychotic-naïve subjects (although numbers were small and the 29% quoted comprised 2 out of 7 subjects). Sandev (1992) determined that 34% of the learning disabled subjects in his study, who were exposed to antipsychotic medication, had evidence of dyskinesia, which was predominantly lingual, perioral and facial in distribution. Similar dyskinetic movements were also observed in two of the six subjects who were antipsychotic-naïve. In a group of 61 women with learning disabilities (Farren and Dinan, 1994), of whom just under half had been exposed to neuroleptics the prevalence of dyskinesia was 64%, although no association with antipsychotic exposure and dyskinesia was found.

Cohen and colleagues found a 17% point prevalence of tardive dyskinesia in 30 learning disabled subjects taking antipsychotics, in contrast to 47% in the group with schizophrenia and no learning disability.

Akathisia does not seem to be a common side effect amongst learning disability patients taking antipsychotic medication (Ganesh et al, 1989; Sandev, 1992), with reported point prevalences of 7% and 3.7% respectively. In contrast, drug-induced Parkinsonism occurs frequently and has been observed to occur in 61% of learning disabled subjects resident in a Welsh institution taking antipsychotic medication (Murti Rao et al, 1989). No subjects in the antipsychotic free control group showed any features of Parkinsonism on the rating scale that was designed for this study.



It has been reported that antipsychotic drugs are frequently used in hospitalised individuals with learning disabilities, many of whom have behavioural disturbances (Fischbaucher, 1987; Brandford, 1996), Gaulteri et al (1986) have suggested that the use of such medications in this population, many of whom have severe and profound learning disabilities, is of unproven value. In recent years this has resulted in concern regarding the use of such drugs in a group of people with an apparently high propensity to develop dyskinesia and drug-induced Parkinsonism (Sande, 1992).

#### 10.1.2 Spontaneous involuntary disorders of movement in people with learning disability.

Before the advent of neuroleptics, Earl (1934) published a review and original article reporting motor abnormalities to be present in almost every subject in a population of 135 males with severe learning disabilities. He suggested that this was similar to the presentation of patients with schizophrenia and sought other similarities between the two conditions. Despite a great deal of literature on disorders of movement in the half a century since Earl made his observation, relatively few studies have considered the prevalence of motor disorders in people with learning disabilities who are not taking antipsychotic medication.

Two studies, one from North America and the other from England, have sought to provide point prevalence figures for movement disorders in large learning disability institution populations (Stone et al, 1989; Rogers et al, 1991).

Stone and colleagues (1989) assessed all available residents (N = 1227) of an institution for people with developmental disabilities for both dyskinesia and Parkinsonism. The majority of subjects had either severe (17%) or profound (73%) learning disability. Dyskinesia was evident in 48% of the sample, dystonia in 29%, akathisia in 13% and Parkinsonism in 3%. The former increased with age and female gender, and the latter increased with age and male gender. Surprisingly, the only significant effect of antipsychotic drug exposure was a positive correlation with akathisia. However, the rating scale used was devised especially for the study and it is therefore uncertain if these findings are comparable with other populations who have been assessed using standardised scales.

The work of Rogers et al (1991) focused on 236 subjects, the majority were men (86.4%) with either severe (23%) or profound learning disability (40%). The population was divided into three groups, those receiving antipsychotics (N=76), those who had previously received antipsychotics (N=61), and those who were antipsychotic-naïve (N=99). Tardive dyskinesia occurred in 34%, 20% and 27% respectively. There were significant positive correlations between motor abnormalities and both the severity of learning disability and a history of epilepsy. Rogers then compared this data to that from a previous study (Rogers, 1985) of long stay institutionalised people with severe psychiatric illnesses (92% with a diagnosis of schizophrenia) which used the same rating scale. He showed a remarkable similarity between the two

populations in terms of the range and frequency of motor abnormalities found, most being extrapyramidal in nature. This finding resonates with the ideas of Earl (1934), formulated when the confounding effects of antipsychotics were irrelevant, regarding a commonality between the movement disorders of severe learning disability and schizophrenia.

Both Stone and colleagues and Rogers studied institutionalised populations and the majority of subjects suffered from either severe or profound learning disabilities. To date, information on spontaneous involuntary movement disorders in people with mild learning disability is limited. The prevalence of spontaneous involuntary motor disorders in this specific group of people is largely unknown.

#### 10.1.2. Spontaneous involuntary disorders of movement in people with schizophrenia.

It is beyond the remit of this thesis to review the extensive literature on antipsychotic-induced involuntary movement disorders in schizophrenia.

However, the occurrence of spontaneous involuntary disorders of movement in people with schizophrenia, who have never received any antipsychotic medication, is of central importance to this study.

For both ethical and practical reasons it has become increasingly difficult to recruit people with schizophrenia, other than those in a first episode, who are antipsychotic-naïve. Yet there are several relatively recent reports in the

literature of people with schizophrenia who are antipsychotic-naïve and show an excess of dyskinetic movements (Demars, 1966; Pryce and Edwards, 1966; Brandon et al, 1971; McCreadie et al, 1982; Owens et al, 1982; Waddington and Youseff, 1990; McCreadie et al, 1997). Both Owens and colleagues (1982) and McCreadie et al (1997) concur that when compared to people with longstanding schizophrenia treated with conventional antipsychotic therapy, unmedicated subjects (who have all been ill for a long period of time) show virtually no significant differences in dyskinesia scores as rated by the AIMS. The only exception is that medicated subjects show a slight excess of upper limb dyskinesia (Owens et al, 1982). Two studies have failed to replicate these results in non-first episode antipsychotic-naïve subjects (Chorfi and Moussaoui, 1989; McCreadie and Ohaeri, 1994). The unmedicated patients in both these studies were however all young and therefore in the relatively early stages of the illness.

Chatterjee et al (1995) assessed 89 first-episode cases of schizophrenia before any received antipsychotic medication, and showed that 16.9% had evidence of extrapyramidal signs. However, only one subject of the 89 assessed showed dyskinesia as rated by the Tardive Dyskinesia Rating Scale.

Given that these subjects were in the first episode of their illness the validity of the diagnosis must remain open to question. The possible role of illicit substance abuse cannot be neglected as a possible aetiological factor for both the physical and psychological presentation of these subjects. Theoretically, abuse of amphetamine derived substances could modify the presentation of

spontaneous disorders of movement. Indeed in combination with antipsychotic medication concomitant substance abuse has also been shown to be a significant risk factor for the development of tardive dyskinesia in people with schizophrenia (Bailey et al, 1997).

Owens et al (1982) suggested that never medicated people with schizophrenia show evidence of involuntary disorders of movement as a consequence of the pathological cerebral process underlying the disease. If we accept that schizophrenia is a brain disease, then the views extended by Marsden (1982) and Rogers (1985) that a dual pathological process may be occurring in unmedicated individuals, implying a secondary undiagnosed neurological disease is present in addition to psychosis, becomes somewhat tautological.

In terms of characterising the nature of schizophrenia in people with pre-morbid mild learning disability the presence of spontaneous involuntary disorders of movement in people with each condition in isolation is of importance. It would seem to imply that a common pathology may underlie the mechanism of production of such movement disorders in both cases. In order to explore this hypothesis further it is necessary to characterise the nature of spontaneous involuntary disorders of movement as they occur in antipsychotic-naïve people with mild learning disability. The effects of antipsychotic medication on movement in co-morbid subjects will also be compared to those apparent in controls with schizophrenia alone.

## 10.2. Method

Three established scales for rating involuntary movements were used to quantify the presence or absence of movement disorders in the study population. The Abnormal Involuntary Movement Scale (AIMS; Guy et al, 1978) provides a rating of dyskinesia in seven body areas, facial muscles, lips and perioral area, jaw, tongue, upper limbs (tremor is not rated), lower limbs and trunk (neck, shoulder and hips). It uses a five point scale (0-4) ranging from absent to severe, for each item. A score of 2 (mild) or more on any item is conventionally taken as confirmation that dyskinesia is present. The specification, "movements that occur upon activation to be rated one less than those observed spontaneously" was not implemented, although activation techniques and reinforcement were routinely used in assessments.

The Targeting Abnormal Kinetic Effects (TAKE; Wojcik et al, 1980) scale provides an assessment of Parkinsonism. It was designed to complement the AIMS and considers bradykinesia, rigidity, tremor, autonomic nervous system effects and akathisia (both subjective and objective components). The five items are scored on a five point scale ranging from absent to severe (0-4).

The Dyskinesia Identification System: Condensed User Scale (Discus; Sprague et al, 1989) is a 15-item dyskinesia rating scale which is a shortened version of the 34-item Dyskinesia Identification System-Coldwater (DIS-Co). It was originally intended for use in populations with developmental disabilities,

but has subsequently been additionally validated in psychiatric populations (Sprague and Kalachnik, 1991; Kalachnik and Sprague, 1993). The items rated are shown in appendix 2. A total score of 5 or above on this scale has been shown to be associated with a reliability of 0.92 in mentally ill populations and 0.91 in learning disability populations (Kalachnik and Sprague, 1993) when compared to the Research Diagnoses for Tardive Dyskinesia (RD-TD; Schooler and Kane, 1982).

Subjects with cerebral palsy (N = 2) or hemiparesis (N = 1) were excluded, two other subjects were uncooperative with testing. A composite examination incorporating all items from the three scales was conducted on each subject (N=96).

Items from the rating scales were coded and entered into SPSS. Descriptive frequencies were obtained for all the items on all three scales. For the AIMS and TAKE numbers and percentages of subjects scoring two or more on each item were derived, in addition to the total score. For the DISCUS numbers and percentages of subjects scoring a total of 5 or more on the whole scale were derived. Fisher's Exact Test was used to investigate between group differences (at a significance levels of  $p < 0.05$  and  $p < 0.01$ ) for total and individual items on the AIMS and TAKE and total items on the DISCUS. Regional item scores were plotted graphically by subject group for the AIMS and TAKE. Group differences in mean scores were assessed by one-way ANOVA with a post-hoc least significant difference test.



The within group effects of gender, epilepsy, and being on depot medication in those people scoring at least 2 on any item of the AIMS or TAKE and at least a total score of 5 on the DISCUS, were explored using Fisher's Exact Test. Mean within group score effects were explored using Student's Independent t-test. Finally Pearson's Product Moment Correlation was used to consider relationships between total scores and age IQ, psychopathology, NES scores, RBMT, MPAs, depot duration and chlorpromazine equivalent dose of antipsychotic medication at the time of the study.

### 10.3. Results

#### 10.3.1 Between group results AIMS, TAKE, DISCUS

Table 24 - Numbers and percentages of subjects in each group attaining significant scores for AIMS, TAKE and DISCUS.

RATING SCALE AND SCORE	LEARNING DISABILITY GROUP (N = 25)		CO-MORBID GROUP (N = 37)		SCHIZOPHRENIA GROUP (N = 34)	
	NUMBER	%	NUMBER	%	NUMBER	%
<b>AIMS</b>						
AT LEAST 2 ON ANY ONE ITEM	7	28%	20	54%	17	50%
FACIAL MUSCLES AT LEAST 2	0	0***^	10	27%	10	29.4%
LIPS AND PERIORAL AT LEAST 2	1	4%	8	21.6%	5	14.7%
JAW AT LEAST 2	2	8%	5	13.5%	6	11.6%
TONGUE AT LEAST 2	2	8%	4	10.8%	3	9.8%
UPPER LIMBS AT LEAST 2	1	4%	2	5.4%	2	5.9%
LOWER LIMBS AT LEAST 2	0	0^	4	10.8%	7	20.6%



RATING SCALE AND SCORE	LEARNING DISABILITY GROUP (N = 25)		CO-MORBID GROUP (N = 37)		SCHIZOPHRENIA GROUP (N = 34)	
	NUMBER	%	NUMBER	%	NUMBER	%
TRUNK AT LEAST 2	2	8%	2	5.4%	4	5.9%
<b>TAKE</b>						
AT LEAST 2 ON ANY ONE ITEM	7	28%**^^	34	91.2%	27	79.4%
BRADYKINESIA AT LEAST 2	3	12%**^^	26	67.4%	18	52.9%
RIGIDITY AT LEAST 2	4	16%**^	26	67.4%^	14	31.2%
TREMOR AT LEAST 2	3	12%*	16	42.1%^^	4	11.8%
AUTONOMIC SIGNS AT LEAST 2	2	8%	3	7.9%	6	17.6%
AKATHISIA AT LEAST 2	0	0^	4	10.5%	7	20.6%
<b>DISCUS</b>						
TOTAL SCORE 5 OR MORE	1	4%*	10	26.3%	8	23.5%

#### Fisher's Exact Test

\* = significantly different to co-morbid group where  $p < 0.05$

\*\* = significantly different to co-morbid group where  $p < 0.01$

^ = significantly different to schizophrenia group where  $p < 0.05$

^^ = significantly different to schizophrenia group where  $p < 0.01$

The results of between group comparison for significant scores of movement disorder (AIMS - score of at least 2 on any item and individual item scores of at least two; TAKE - score of at least 2 on any item and individual item scores of at least two; DISCUS - total score of at least 5) are shown in table 24. The results are also presented graphically in figure 9 (AIMS) and figure 10 (TAKE), where each bar represents the percentage of subjects who score 2 (mild) or more on each variable. The individual AIMS scores were then sub-divided into four categories; face (comprising ratings of facial muscles, lips and perioral area, jaw and tongue), extremities (comprising ratings of upper and lower limbs) and trunk (comprising the unaltered single trunk rating). A one-way

ANOVA with a post-hoc least significant difference test was then conducted on the mean scores of these sub-categories to enable between group comparisons.

Figure 9 - Percentage scoring  $\geq 2$

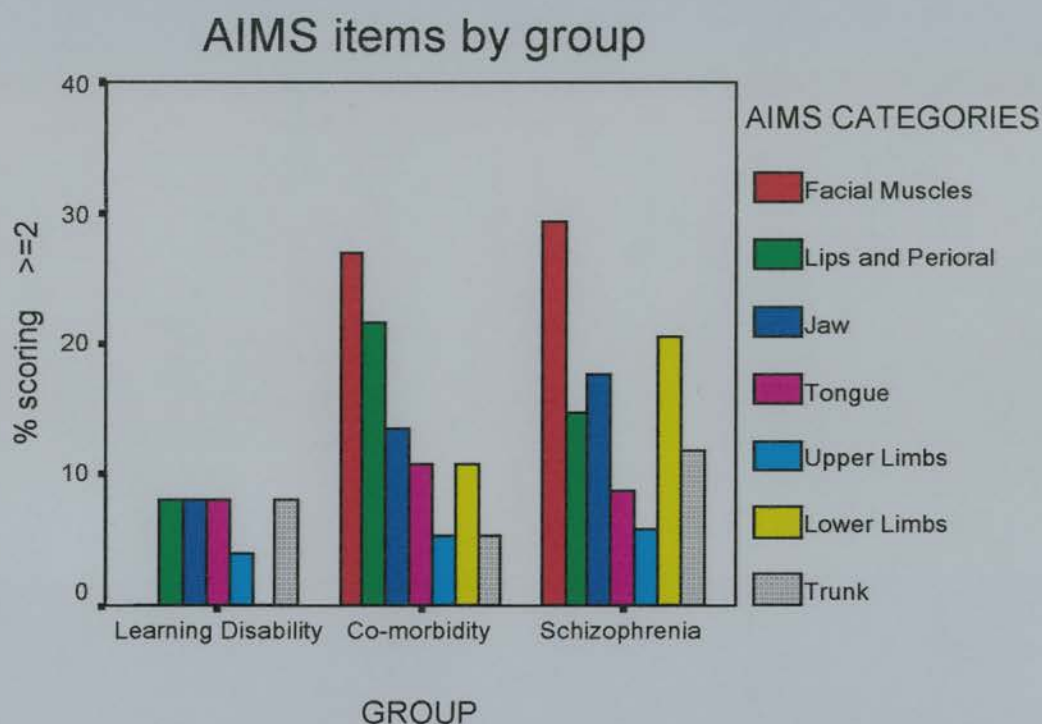
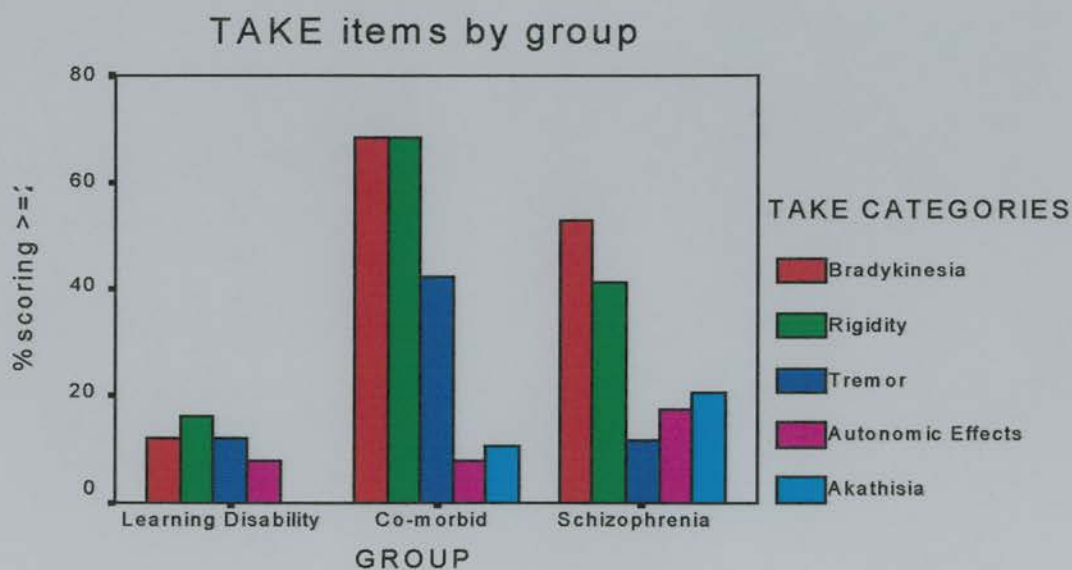


Figure 10 - Percentage scoring  $\geq 2$  on



The co-morbid group had a significantly higher mean score on the face sub-category than the learning disability control group (2.20 s.d. 2.3 vs. 0.72 s.d. 2.2;  $p = 0.019$ ). Subjects with schizophrenia alone had a significantly higher mean extremities score than people with mild learning disabilities (0.82 s.d. 1.7 vs 0.008 s.d. 0.4;  $p = 0.019$ ). No differences between the mean scores of the three groups were noted in the trunk sub-category.

#### 10.3.2 The effects of gender, epilepsy and depot antipsychotic medication on involuntary movements.

Fisher's Exact Test showed no significant effects of gender or epilepsy on the numbers of subjects in each group who score 2 or more on any item on the AIMS or TAKE. Similarly, there are no significant differences seen dependent on whether or not the subjects in the co-morbid and schizophrenia groups were taking depot medication at the time of assessment. Gender, epilepsy and depot medication have no effect on the number of subjects who score 5 or more on the total DISCUS score as determined by Fisher's Exact Test.

When considering individual item scores, no effects of gender are seen. However, co-morbid subjects with epilepsy are significantly more likely to score 2 or more on the jaw movement item of the AIMS relative to co-morbid subjects with no history of epilepsy (Fisher's Exact Test;  $p = 0.01$ ). In the learning disability group people with a history of epilepsy are more likely to score 2 or above on the item rating tremor in the TAKE, than those without epilepsy (Fisher's Exact Test;  $p = 0.028$ ).

The effects of taking depot medication at the time of assessment on individual items in the co-morbid and schizophrenia groups were then considered. People in the co-morbid group taking depot medication were more likely to score 2 or above on the bradykinesia item of the TAKE, this was not replicated in the schizophrenia control group (Fisher's Exact Test;  $p = 0.033$ ).

The effects of gender, epilepsy and depot medication on the mean scores of the AIMS, TAKE and DISCUS total and sub-scores were then considered using a Student's independent t-test. Male schizophrenia controls had a higher total mean score on the DISCUS (4.37 s.d. 4.4) than female schizophrenia controls (1.47 s.d. 2.9;  $t = 2.20$ , d.f. 32,  $p = 0.035$ ). Learning disability subjects with a history of epilepsy had a significantly higher mean TAKE total score (2.88 s.d. 2.6) than those with no history of epilepsy (0.75 s.d. 1.6;  $t = -2.51$ , d.f.=22,  $p=0.02$ ). No significant effect of depot medication on any mean scores were seen in either the schizophrenia or co-morbid groups.

#### 10.3.3 Relationship between age, IQ, psychopathology, RBMT SP score, NES total score, MPAs, chlorpromazine equivalent dose of medication and involuntary movements.

Firstly, the within group relationships of these variables to movement disorders were explored in each of the three groups using a Student's independent t-test on the cut-off scores of the three tests described above. The only significant

difference to emerge was that of a higher mean NES total score (35.0) in the one person with learning disability alone who scored 5 or more on the total discus score compared to the remaining 24 subjects who scored less than 5 (17.9 s.d. 7.4;  $t = -2.26$ , d.f. = 23,  $p = 0.033$ ).

Secondly, Pearson's Product Moment Correlations were conducted on total AIMS, TAKE and DISCUS scores, age, age at first symptoms, NART and Quick IQ tests, symptom clusters of the PANSS, RBMT SP score, NES total and sub-total scores, weighted and unweighted Waldrop scores, current chlorpromazine equivalent dose of antipsychotic medication and total time on depot medication. The significant results of these correlations are shown in figure 25.

Figure 25 - Significant Pearson Correlations between involuntary movement disorders age, age at first psychotic symptoms IQ, psychopathology, memory, NSS, MPAs and antipsychotic medication usage.

<u>MOVEMENT DISORDER RATING</u>	<u>MILD LEARNING DISABILITY GROUP</u> (r and p values)	<u>CO-MORBID GROUP</u> (r and p values)	<u>SCHIZOPHRENIA GROUP</u> (r and p values)
<u>AIMS TOTAL SCORE</u>	DISCUS TOTAL SCORE (0.956, $p < 0.001$ )	DISCUS TOTAL SCORE (0.795, $p < 0.001$ )	DISCUS TOTAL SCORE (0.883, $p < 0.001$ )
	NEGATIVE SYMPTOMS (PANSS) (0.753, $p < 0.001$ )		
	PRIMITIVE REFLEXES (NES) (0.760, $p < 0.001$ )	PRIMITIVE REFLEXES (NES) (0.475, $p = 0.004$ )	
	SENSORY INTEGRATION (NES) (0.421, $p = 0.041$ )	SENSORY INTEGRATION (NES) (-0.382, $p = 0.034$ )	

<u>MOVEMENT DISORDER RATING</u>	<u>MILD LEARNING DISABILITY GROUP</u>  (r and p values)	<u>CO-MORBID GROUP</u>  (r and p values)	<u>SCHIZOPHRENIA GROUP</u>  (r and p values)
<u>AIMS TOTAL SCORE</u>	TOTAL NES SCORE (0.469, p=0.018)		
		TAKE TOTAL SCORE (0.579, p=<0.001)	
<u>DISCUS TOTAL SCORE</u>	NEGATIVE SYMPTOMS (PANSS) (0.680, p=<0.001)		
	PRIMITIVE REFLEXES (NES) (0.774, p<0.001)	PRIMITIVE REFLEXES (NES) (0.347, p=0.038)	
	SENSORY INTEGRATION (NES) (0.449, p=0.028)		
	TOTAL NES SCORE (0.473, p=0.017)		
		TOTAL TIME ON DEPOT (0.437, p=0.006)	
<u>TOTAL TAKE SCORE</u>	NO CORRELATIONS	PRIMITIVE REFLEXES (NES) (0.432, p=0.009)	MOTOR CO- ORDINATION (NES) (0.345, p=0.05)
		TOTAL TIME ON DEPOT (0.393, p=0.015)	

## 10.4 Discussion

### 10.4.1. Methodological issues

One of the main difficulties in the interpretation of these results is that the author was not blind to the diagnoses of subjects at the time of the movement disorder assessment. Furthermore, in many cases the author was also aware of the current medication regime of the subject. This was unavoidable as each subject was selected and approached by the author with regard to their participation in the study and casenotes had been scrutinised prior to this initial approach in all cases. It is unknown to what extent this may have biased the

overall results. Due to the time constraints on this study only one examination for movement disorders could be undertaken for each subject, the temporal consistency of these ratings are therefore unknown.

Another methodological consideration is that of the assessment of both the subjective and objective components of akathisia (Lancet, 1986) in people with learning disabilities. This point has been raised by Ganesh and colleagues (1987) who alluded to the difficulties experienced in obtaining a subjective report of restlessness in people with moderate, severe or profound learning disabilities. In the present study the author experienced no difficulties in obtaining a subjective report of akathisia from subjects with either mild learning disability or co-morbidity. Furthermore, the subjective account of restlessness given by individuals in this study was invariably congruent with the objective motor manifestations of akathisia.

#### 10.4.2 Between group differences and similarities

28% of subjects with no history of antipsychotic usage and mild learning disability, have dyskinesia as rated by scoring at least 2 or more on one item of the AIMS. This is comparable with the findings of Rogers and colleagues (1991) where 27% of subjects with learning disability and no history of antipsychotic drug use were found to have dyskinesia. However, only 4% of the subjects in the present study score a total of 5 or more on the DISCUS, a more area specific measure of dyskinesia, specifically designed for use in people with developmental disabilities.



Perhaps more important than raw percentages, is the fact that there are no differences in the numbers of subjects attaining significant AIMS and DISCUS scores in both the mild learning disability group and group of schizophrenia controls (table 24 and figure 9). If a level of significance of  $p=0.01$ , is assumed then there are also no differences in the numbers of subjects with significant AIMS and DISCUS scores in the mild learning disability group and co-morbid group.

From these figures two inferences are possible. Firstly, that involuntary disorders of movement, in the form of dyskinesia, occur in people with mild learning disability who have not been exposed to antipsychotics and also in people with mild learning disability who have been exposed to antipsychotics (by virtue of having schizophrenia), to the same degree. Therefore, in people with schizophrenia and a normal pre-morbid IQ, exposed to antipsychotic medication, where dyskinesia is seen to the same extent as in the co-morbid group, this dyskinesia is not attributable to the effects of medication.

Secondly, if the dyskinesia seen in people with schizophrenia and a normal pre-morbid IQ is spontaneous and independent of the effects of antipsychotic medication (as suggested by the correlational data) then a spontaneous dyskinesia of a similar nature is also present in people with mild learning disability and no psychosis.



There are two significant differences in the AIMS scores of people with mild learning disability relative to other groups. Firstly, people with mild learning disability have no significant dyskinesia of muscles of facial expression, these are found in both the co-morbid and schizophrenia groups to the same extent. There are no differences in the mean amounts of chlorpromazine equivalent medication these two groups were receiving at the time of the study.

Secondly, people with mild learning disability have no abnormal movements of the lower limbs, this is not significantly different to people with co-morbidity. However, 20.6% of schizophrenia controls do show evidence of abnormal lower limb movements, these findings parallel those for the rating of akathisia on the TAKE.

Roger's (1991) study of people with learning disabilities showed that akathisia was the only movement disorder correlated with antipsychotic exposure in this population. Furthermore, Ganesh et al (1987) demonstrated that the rate of akathisia in people with learning disability, when given antipsychotics, was lower than may be expected in the normal population exposed to antipsychotic medication. The findings of this study are consistent with both of these authors.

It is therefore proposed that differences between groups in terms of muscles of facial expression and lower limb movements may be accounted for by the effects of antipsychotic medication. However, it is proposed that all other items rating significantly on the AIMS are spontaneous involuntary disorders of

movement. Spontaneous lingual-facial-buccal dyskinesia is stated to occur in 0.8% of normal healthy people between the ages of 50-55 years (Klawans and Barr, 1982). Therefore, findings such as these in subjects whose mean age is 48 years is most unusual and around 50 times more frequent than expected in the normal population.

The between group scores on the TAKE, which measures Parkinsonian signs, (table 24 and figure 10) show a very different pattern to those of the AIMS. Although the learning disability group do score significantly on all items of the scale, except akathisia, significantly fewer score on this scale than either other group ( $p < 0.01$ ).

People exposed to antipsychotic medication with co-morbidity and schizophrenia are much more likely to score significantly for bradykinesia and rigidity ratings than people with mild learning disability, not exposed to antipsychotics. Furthermore a greater percentage of people in the co-morbid group score significantly on the rigidity and tremor items than the schizophrenia control group ( $p < 0.05$  and  $p < 0.05$ ), suggesting they may be more susceptible to these extrapyramidal effects of antipsychotic medication than people with no pre-morbid cognitive impairment. This is substantiated by the correlational data (figure 25) which demonstrates the co-morbid total TAKE score correlates positively with the total time the subject has taken depot antipsychotic medication ( $r = 0.393$ ,  $p = 0.015$ ). No such correlation is seen in the schizophrenia control group.

It has been stated that one of the two between group difference in the AIMS score is in movements of muscles of facial expression. The finding that the composite score of facial items derived from the AIMS, has a significantly higher mean score in the co-morbid group further supports the view that co-morbid subjects are particularly vulnerable to the effects of antipsychotic medication.

#### 10.4.3. The effects of gender and epilepsy.

There are no gender effects on any of the AIMS or TAKE scores. When considering the DISCUS, a more region specific assessment tool for dyskinesia than the AIMS, male schizophrenia controls have higher total mean scores than females. The use of the DISCUS in this non-learning disabled population may highlight dyskinesias associated with abnormal neurodevelopment. It was originally devised for use in a learning disabled population. This finding perhaps indicates, in a similar fashion to an excess of NSS in males with learning disabilities (reported in chapter eight), that men are more susceptible to neurodevelopmental dyskinesias than women. The effect is perhaps not seen in the learning disabled populations because such gender differences, in these generally developmentally compromised groups, are less extreme.

Considering the effect of a history of epilepsy on movement disorders in the co-morbid and learning disability groups, people with co-morbidity and epilepsy show more dyskinetic jaw movements (AIMS) than co-morbid subjects without

epilepsy. People with learning disability and epilepsy show more tremor (TAKE) than learning disability controls with no epilepsy history. This may help to explain why more co-morbid subjects have evidence of significant tremor than people with schizophrenia alone, a greater proportion of people with co-morbidity have a history of epilepsy (chapter seven). These effects may relate to the use of anticonvulsant medication. In addition, van Emmerik and colleagues (1993) have shown that people with learning disabilities show evidence of more physiological tremor per se than normal healthy controls.

It may be that those people with epilepsy have a greater degree of cerebral dysfunction than people without and this renders them more susceptible to adverse extrapyramidal effects of antipsychotic medication. Although in a study of antipsychotic induced Parkinsonism, in people with more severe learning disabilities than in the present study, Murti Rao and co-workers (1989) found no association between overt brain damage and Parkinsonism scores.

#### 10.4.4. Relationship with age, IQ, psychopathology, memory, NSS, MPA, antipsychotic medication and involuntary movement disorders.

There are no correlations with current age or age at first symptoms of psychosis and AIMS, TAKE or DISCUS total scores in any of the groups in this study. Similarly, there are no correlations with total movement disorder scores and the results of the NART or Quick IQ test in any of the groups (the NART was only performed in schizophrenia controls).

Studies of people with longstanding schizophrenia and no history of pre-morbid cognitive impairment have found a positive correlation between age and dyskinesia (Soni et al, 1993), a negative correlation between IQ and dyskinesia (Waddington and Youseff, 1986; Manschreck et al, 1990; Brown and White, 1991) and no correlation between IQ and dyskinesia (Soni et al, 1993). None of these studies included people with pre-morbid IQ's outwith the normal range.

Unlike some other studies of movement disorders in people with schizophrenia (Brown and White, 1991; Manschrenck et al, 1990) this study found no association between movement disorders and negative symptoms in either the co-morbid or schizophrenia groups. It does however concur with the work of McCreddie and colleagues (1997). In a population of antipsychotic-naïve Indian people with schizophrenia they found no significant associations between negative symptoms, as rated by the PANSS, with dyskinesia, as rated by the AIMS. They found no significant association with memory ability and AIMS scores and this is also replicated by the present study when the results of the RBMT SP score are considered.

The correlations seen in the learning disability and co-morbid group between primitive reflexes, as measured by the NES, and AIMS and DISCUS total scores may in part be explained by the inclusion of the glabellar tap in the NES as a primitive reflex. It may also indicate a greater degree of cerebral

dysfunction, especially of the frontal lobe, in the learning disabled group relative to the schizophrenia control group, where no such correlation is seen.

As noted previously in chapter eight, it is intriguing that depot medication appears to improve the performance of co-morbid subjects on the sensory integration sub-scale of the NES. A variant of this effect is seen again when correlations with AIMS total scores are considered. A positive association between NES sensory integration scores and AIMS score is seen in the learning disability antipsychotic free group, whereas a negative correlation is seen in the co-morbid group and no association in the schizophrenia group.

It almost appears that antipsychotic agents modify the faulty mechanism producing sensory integration difficulties in people with co-morbidity and that the occurrence of this is intrinsically linked to the mechanism producing spontaneous involuntary movements in these individuals. These deficits in sensory integration are not so marked in people with schizophrenia and no pre-morbid cognitive impairment, but are improved by the administration of depot rather than oral antipsychotics (chapter nine).

There are no significant correlations between MPAs, as rated by the Waldrop scale (both weighted and unweighted) and movement disorders. Similarly, there are no associations between chlorpromazine equivalent doses of medication and total movement disorder scores. There is a significant positive correlation with total time on spent on depot medication and both DISCUS and

In terms of the TAKE scores in the co-morbid group. As stated above, perhaps this reflects a greater propensity to develop both orofacial dyskinesia and Parkinsonian signs when people with pre-morbid cognitive impairment and schizophrenia are treated with antipsychotic medication.

### 10.6 Conclusions

People with mild learning disability who have never been exposed to antipsychotic medication show evidence of spontaneous involuntary disorders of movement, in the form of dyskinesias, to the same degree as co-morbid subjects and schizophrenia controls. Other studies have shown spontaneous involuntary disorders of movement to occur in people with schizophrenia who are antipsychotic-naïve (e.g. Owens et al, 1982). It has been suggested that there may be a degree of overlap between the movement disorders seen in severe learning disability and schizophrenia (Earl, 1934; Rogers et al, 1991).

This study has shown that the same is also true of mild learning disability and co-morbidity, in relation to schizophrenia in the normal population. The spontaneous dyskinesias that occur in all three groups are not related to age, gender, pre-morbid or morbid IQ, symptomatology, memory function, epilepsy, antipsychotic medication or the age of onset of psychosis. As such it is suggested that there is a common aetiology for these dyskinesias in people with schizophrenia and people with mild learning disability and co-morbidity.

In terms of the Parkinsonian effects of antipsychotic medication people with co-morbidity appear to be particularly vulnerable to the development of these, which are more clearly linked to the duration of time an antipsychotic medication is given, rather than the dose at the time of assessment.



## CHAPTER ELEVEN

### THE VINELAND ADAPTIVE BEHAVIOUR SCALES

*“As by dementia praecox what is remembered is less injured than the ability to use it, we often still find surprising knowledge, while efficiency has suffered most severe losses. Imbeciles on the contrary can often manage fairly well in their daily tasks, even when their knowledge is of the very lowest degree.”*

Kraepelin 1919

#### 11.1 Introduction

##### 11.1.1 Development of the concept of adaptive behaviour

The North American special needs education system underwent a period of rapid transition from the 1950s to 1970s. In part this was augmented by the election of John Kennedy in 1961, whose learning disabled sibling focused media attention on provisions for people with learning disabilities. New legislation emphasising training, as opposed to custodial care, for people with mental retardation was instigated. To compliment these training regimes, regular progress assessments were required, by law, to monitor newly acquired skills. Adaptive behaviour scales were sought to provide such objective assessments and rapidly became established as valuable assessment instruments, when used in tandem with conventional IQ tests (Horn and Fuchs, 1987).

The Vineland Social Maturity scale (Doll, 1953). challenged long held assumptions that low IQ was the sole factor responsible for social incompetence. Over the following 20 years interest in adaptive behaviour scales and their use in the assessment of people with learning disabilities and

mental retardation (in North American terminology) grew. The American Association on Mental Deficiency incorporated social adaptation constructs into its definition of mental retardation (Grossman, 1983) in the middle of the 1970s and the concept of intellectual disability broadened as a result. It has been stated that the use of adaptive behaviour assessments played a pivotal role in the 'normalisation' of people with special needs in the United States (Coulter and Morrow, 1978). The use of these scales, in addition to IQ tests, was believed to improve the construct validity of the diagnosis of intellectual impairment.

In the education system, the use of adaptive behaviour scales for determination of entry to, or removal from (declassification), special education provoked a great deal of debate. Children with IQ scores below 70, but with normal adaptive behaviours, no longer qualified for special education in many areas. The reliance of adaptive behaviour scales on racial and ethnically determined societal norms was considered to be potentially disadvantageous to minority groups. This resulted in a revision of adaptive behaviour scales to place greater emphasis on age appropriate skills. These became viewed as goals which were to be accomplished before a child could be integrated into mainstream facilities and provided a checklist of societal expectations (Witt and Martens, 1984). The use of adaptive behaviour measures gradually became of special importance in the identification of people with mild degrees of mental impairment (Patton, 1986), as subtle practical dysfunction could be objectively determined.

### 11.1.2 Definitions of adaptive behaviour

There has been great difficulty in producing a unified definition of adaptive behaviour (McGrew and Bruininks, 1990). The American Association on Mental Deficiency has defined adaptive behaviour as;

*"limitations in an individual's effectiveness in meeting the standards of maturation, learning, personal independence and/or social responsibility that are expected for his/her age level"*

(Grossman, 1983).

As this definition implies by the inclusion of the term 'expected', adaptive behaviour may be modified by cultural influences of a racial or ethnic nature. The capacity of the individual to respond to the demands of their immediate environment is also emphasised. such an interaction with the 'here and now' will obviously alter as the individual ages. For these reasons the concept of adaptive behaviour is considered to be relative and dynamic, as opposed to absolute and static (Horn and Fuchs, 1987).

Factor analytic studies have attempted to differentiate more precisely the dimensions of adaptive behaviour. The main distinction which emerges from this statistical work is between factors relating to specific skills and abilities necessary to maintain personal independence, and factors relating to motivational attributes influencing self initiation (Bruininks et al, 1987).

Today, the Vineland Adaptive Behaviour Scales are one of the most commonly used measures of adaptive behaviour, of which more than 100 exist (Meyers et

al, 1979). The manual for these scales defines adaptive behaviour as, 'the performance of the daily activities required for personal and social sufficiency' (Sparrow et al, 1984b). Three main principles relating to the construct of adaptive behaviour are emphasised; that it is age related, it is defined by the standards and expectations of other people, and finally that it is defined by typical performance and not ability.

### 11.1.3. The relationship between adaptive behaviour and IQ assessment

The relationship between adaptive behaviour and intelligence has not been clearly defined (Keith et al, 1987). There are intrinsic similarities between the two e.g. an ability to cope with the environment is central to and implicit in the constructs of both (Adaptive Behaviour: Sparrow et al, 1984b; IQ: Weschler, 1974). However, it is possible for the same individual to perform above the average level on one, yet poorly on the other. For this reason, adaptive behaviour and IQ are regarded as being categorically distinct (Atkinson, 1990).

Kamphaus (1987) has stated that the construct validity of adaptive behaviour scales may be examined by study of the pattern of correlation shown with standardised IQ tests. If this correlation is greater than 0.5, then he suggests that the validity of the adaptive behaviour scale used should be questioned. Generally, correlations between adaptive behaviour and assessments of intelligence range from 0.4-0.6 (Reschley, 1982). The Vineland Adaptive Behaviour Scales show a correlation of 0.52 with the WISC for a sample of emotionally disturbed children (Sparrow et al, 1984b).

Research in adaptive behaviour has focused largely on differences between groups of individuals. These have included differences between race and ethnic groups of children (Sparrow et al, 1984b), between diagnostic groups within the learning disability spectrum (Foster and Nihira, 1969), and between groups of people with learning disabilities, who have been placed in different residential settings (Conroy et al, 1982).

#### 11.1.4 The use of the Vineland Adaptive Behaviour Scales (VABS) in the study population.

In people with mild learning disability the role of the VABS is firmly established. It may be used to identify learning disabilities, particularly in children where educational placement decisions may depend upon adaptive behaviour assessment, to devise individual programmes and assess the efficaciousness of these, and also to compare different populations to enable service provision planning (Bruininks et al, 1987).

Although the VABS is most commonly used in children under the age of 19, it may also be used to assess adaptive behaviour of non-handicapped individuals from birth to 19 years of age and 'low functioning adults' (Sparrow and Cicchetti, 1985)

In people with co-morbidity, the VABS provides a more specific measure of ability than a solitary numerical assessment of IQ. An IQ score offers little

information regarding the impact of illness on every day functioning and does not discriminate between people with mild learning disabilities alone and people with co-morbidity. Therefore, it is hoped that by using the VABS in the co-morbid population, additional impairments consequent upon illness, rather than pre-morbid cognitive impairment may be differentiated by comparison to the learning disability control group.

With the notable exception of standardisation with the normal population, the VABS are rarely used in people who do not have evidence of, or are suspected of having learning disabilities. Although the VABS is not a standard method of assessment of functioning in people with schizophrenia, it could potentially provide a practical assessment of areas of everyday difficulty. This may be of particular benefit to people who show predominantly negative symptoms. In many of these patients, where self-motivation is low, lack of volition and social withdrawal are cardinal features of the illness. Assessment of adaptive behaviour may offer the possibility of goal-directed behavioural therapeutic input for individuals with severe and enduring schizophrenia. This may be of value in rehabilitative settings.

In the present context, it is suggested that direct comparison of people with co-morbidity and people with schizophrenia and a normal pre-morbid IQ, may offer further information about the nature of the cognitive impairment that has been observed to occur in people with schizophrenia.

## 11.2. Method

The Vineland Adaptive Behaviour Scale (VABS) was administered to either a relative or carer of each subject. The informant was nominated by the subject and then contacted by the investigator with subject's consent. The VABS survey form (Sparrow et al, 1984a) provides a general assessment of adaptive behaviour and is one of the three versions of the VABS. It takes the form of a semi-structured interview that takes 30-60 minutes to complete. The subject is rated by an informant's account on each of 261 items. The VABS measures functioning in a range of domains which are sub-divided into constituent sub-domains i.e. Communication (receptive, expressive, written sub-domains), Daily living skills (personal, domestic, community sub-domains), Socialisation (interpersonal, play and leisure time and coping sub-domains). The motor scale, with fine and gross sub-domains, and the maladaptive behaviour domain are optional and were not used in this study.

Raw scores for each domain and sub-domain were derived, entered into a database and then the SPSS statistical package. Neither the standard domain scores nor the adaptive behaviour composite were derived. This was because the conversion procedure necessitates reference to standardised population means and assumes homogeneity of study populations. There are no standardised population means that could be suitably applied to people with schizophrenia with no history of learning disability. As a comparison between three independent groups was to be the main objective of the VABS

assessments in this study, reference to standardised means was not considered applicable.

Between group differences in mean scores were assessed by one-way ANOVA with post-hoc least significant difference test. Within group differences in the co-morbid group and schizophrenia control group between the sexes, people with and without epilepsy, and people on depot medication and those on oral preparations, were investigated using Student's independent t-test. Pearson's product moment co-efficient was calculated to consider correlations within groups between age, total time in hospital, IQ, psychopathology, NSS, MPAs, movement disorders, current chlorpromazine equivalent and duration of depot medication.

### 11.3. Results

#### 11.3.1. Between group similarities and differences.

A VABS assessment was performed for 97 subjects of the 101 in the study. An assessment was obtained for all learning disability controls (N=28). In the co-morbid group, one individual did not wish an informant to be involved in the study, VABS assessments were therefore obtained for 38 subjects. In the schizophrenia control group, one subject did not wish an informant to be contacted and an informant could not be identified for two subjects. 31 VABS assessments were conducted in this group. The mean scores (the lower the score the greater the degree of dysfunction in that domain or sub-domain) and



standard deviations for the three domains and nine sub-domains for each group are shown in table 26, significant group differences were derived using a one-way ANOVA with post-hoc LSD

Table 26 – Mean scores, standard deviations and ranges for domains and sub-domains of the VABS by group.

<u>VABS DOMAINS AND SUB-DOMAINS</u> (full possible range)	<u>LEARNING DISABILITY</u> (N=28)		<u>CO-MORBID GROUP</u> (N=38)		<u>SCHIZOPHRENIA GROUP</u> (N=31)	
	Mean	s.d.	Mean	s.d.	Mean	s.d.
	(observed range)		(observed range)		(observed range)	
<u>TOTAL COMMUNITY</u> (0-134)	101.6	13.1	98.1	16.0	<u>126.5*</u>	9.9
	(70-129)		(51-124)		(98-134)	
RECEPTIVE (0-26)	25.1	1.3	<u>24.4*</u>	1.6	25.4	1.0
	(21-26)		(20-26)		(22-26)	
EXPRESSIVE (0-62)	56.8*	5.0	54.2*	6.6	<u>60.7*</u>	1.8
	(36-62)		(27-62)		(56-62)	
WRITTEN (0-46)	19.7	10.8	19.5	11.3	<u>40.5*</u>	7.9
	(3-41)		(0-38)		(16-46)	
<u>TOTAL DAILY LIVING SKILLS</u> (0-184)	150.0	22.4	137.9	25.5	<u>164.8*</u>	18.4
	(80-177)		(56-181)		(121-184)	
PERSONAL (0-78)	73.3	6.6	70.7	7.9	<u>75.7*</u>	3.4
	(50-78)		(37-78)		(68-78)	
DOMESTIC (0-42)	30.3	8.4	<u>24.2*</u>	10.3	34.9	8.6
	(11-42)		(4-42)		(9-42)	
COMMUNITY (0-64)	46.5	10.1	42.9	11.5	<u>54.2*</u>	8.1
	(19-60)		(13-61)		(34-64)	
<u>TOTAL SOCIALISATION</u> (0-132)	103.4^	13.7	94.7	19.0	<u>109.0^</u>	14.8
	(64-123)		(55-132)		(72-132)	
INTERPERSONAL (0-56)	44.1	5.5	40.6	7.3	44.4^	6.6
	(31-50)		(27-56)		(31-56)	
PLAY AND LEISURE (0-40)	31.8	4.5	<u>28.1*</u>	6.6	32.3	5.6
	(20-40)		(17-40)		(21-40)	
COPING SKILLS (0-36)	27.8	6.9	25.9	7.9	<u>32.1*</u>	5.4
	(12-36)		(6-36)		(16-36)	

## One Way ANOVA with post-hoc LSD

^ significantly different to co-morbid group at level of  $p < 0.05$

\*significantly different to both other groups at level of  $p < 0.05$

Between group differences at a significance level of  $p < 0.05$  are found in all domains and sub-domains.

Figure 11 represents the mean domain scores in all three groups graphically. Figures 12-14 demonstrate the distribution of these scores within groups by plotting the cumulative percentage of scores by group.

### 11.3.2 The effect of gender, depot medication and epilepsy on the VABS within groups.

Student's independent t-test was used to investigate the effect of gender on all VABS scores within groups. There were no significant effects of gender on any domains or sub-domains in either the co-morbid group or learning disability control group. Table 27 shows the domains and sub-domains of the VABS in which women perform significantly better than men in the schizophrenia control group. Men did not perform better than women in any domain or sub-domains.

There are no significant differences in the mean scores of any domain or sub-domain of the VABS in any group, when those people receiving depot medication are compared to those receiving oral medication. Similarly, there are no within group differences between those people with a history of epilepsy compared to those without a history of epilepsy, in any of the domains or sub-domains of the VABS.

Table 27 – Significant gender differences in people with schizophrenia and no pre-morbid learning disability on the domains and sub-domains of the VABS.

<u>DOMAINS AND SUB-DOMAINS</u>	<u>MALE SCORE</u> (N=17)		<u>FEMALE SCORE</u> (M=14)		<u>t-test</u> d.f.=29 p value
	Mean	s.d	Mean	s.d	
DAILY LIVING SKILLS TOTAL SCORE	155.1	19.7	176.6	5.5	<0.001
PERSONAL	74.3	3.9	77.3	1.4	0.011
DOMESTIC	30.4	9.4	40.3	2.8	0.001
COMMUNITY	50.4	8.7	58.9	3.9	0.002
SOCIALISATION TOTAL SCORE	103.3	16.1	116.0	9.5	0.014
INTERPERSONAL	42.1	6.5	47.7	5.3	0.014
COPING SKILLS	29.9	6.4	34.9	6.4	0.008

11.3.3 Correlations between the VABS and age, IQ, days spent in hospital, psychopathology, RBMT SP score, NSS, MPAs, movement disorders and chlorpromazine equivalent medication dose.

The significant Pearson product moment correlations for the domains of the VABS, with the above specified study parameters are group are shown in table 28.

Partial correlations to control for the effects of IQ on the positive correlations seen in all three groups with the RBMT SP scores were performed. This was necessary because it has already been established that the RBMT SP scores correlate significantly with Quick IQ in all three groups (chapter seven). When these partial correlations are performed only one significant positive correlation remains with the RBMT SP score. This is in the co-morbid group, where RBMT SP score correlates with daily living skills ( $r=0.348$ ,  $p=0.044$ ).

Figure 11 - Mean VABS domain scores by group

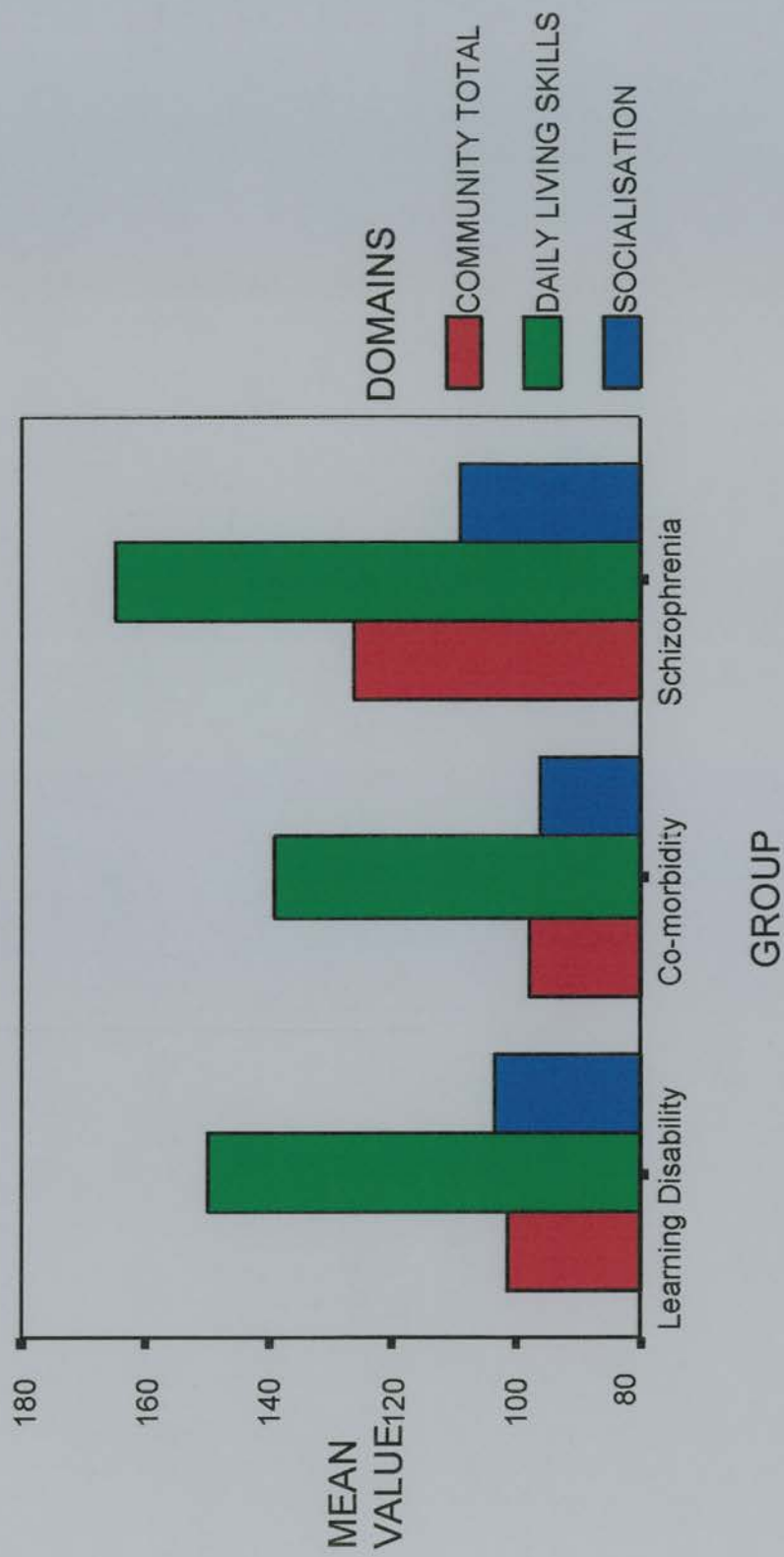


Figure 12- Total community domain score

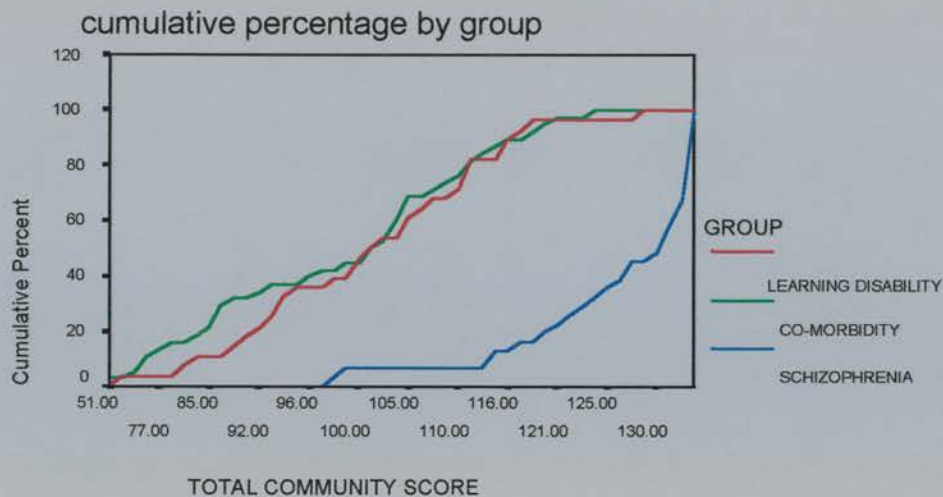


Figure 13 - Total daily living skills domain

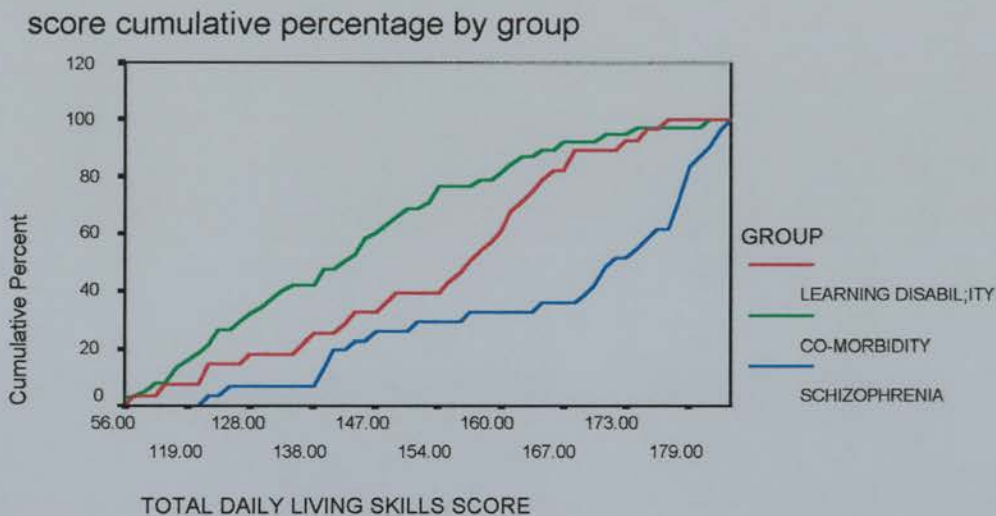


Figure 14-Total socialisation score domain

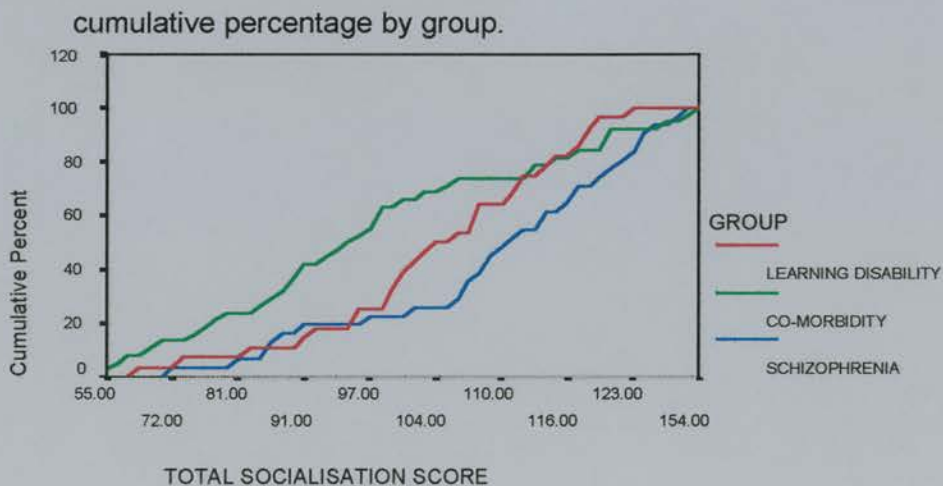


Table 28 -Significant Pearson correlations between VABS domains and age, IQ, psychopathology, memory, NSS, MPAs, movement disorders and medication.

<u>VABS DOMAINS AND SUB-DOMAINS</u>		<u>LEARNING DISABILITY (N=28) r and p values</u>	<u>CO-MORBID GROUP (N=38) r and p values</u>	<u>SCHIZOPHRENIA GROUP (N=31) r and p values</u>
TOTAL COMMUNITY	Positive correlation	RBMT SP score (.419, p=0.03)	Quick IQ (.455, p=0.006)	Quick IQ (.529, p=0.003) RBMT SP score (.651, p=<0.001)
	Negative correlation	Negative symp. (-.504, p=0.012)  DISCUS (-.465, p=0.019) AIMS (-.498, p=0.011)		Positive sympt. (-.501, p=0.004) Negative sympt. (-.416, p=0.020) General sympt. (-.483, p=0.004) Waldrop score (Unweighted) (-.445, p=0.012) CPZ equivalent (-.779, p=<0.001)
TOTAL DAILY LIVING SKILLS	Positive correlation		RBMT SP score (.388, p=0.044)	
	Negative correlation	Negative symp. (-.531, p=0.008) AIMS (-.757, p=<0.001) TAKE (-.418, p=0.038)	Negative sympt (-.459, p=0.004)  TAKE (-.368, p=0.025)	Days in hospital (-.394, p=0.034) Positive sympt. (-.501, p=0.004) Negative sympt. (-.514, p=<0.001) General sympt. (-.483, p=0.006)
TOTAL SOCIALISATION	Positive correlation			Quick IQ (.376, p=0.040) RBMT SP score (.383, p=0.034)
	Negative correlation	Negative symp. (-.653, p=0.001) DISCUS (-.588, p=.002) AIMS (-.664, p=<0.001) TAKE (-.478, p=0.016)		Days in hospital (-.404, p=0.027) Positive sympt. (-.451, p=0.011) Negative sympt. (-.695, p=<0.001) General sympt. (-.632, p=<0.001) CPZ equivalent (-.517, p=0.003)

## 11.4. Discussion

### 11.4.1 Methodological issues

Intrinsic to the philosophy of adaptive behaviour is the concept that usual performance and not ability is ascertained. In this group of subjects many of the people suffering from schizophrenia reported higher levels of functioning prior to the onset of illness e.g. a subject who graduated with a first class degree prior to onset was unable to write a letter as a consequence of distractions from auditory hallucinations, this had been the case for a number of years. His proficiency in literacy skills had previously been proven, yet his level of performance at the time of the study did not reflect this. In contrast, a minority of people with learning disability and co-morbidity were unable to read or write, these skills never having been acquired. The VABS makes no distinction between these two examples, the criterion on which they are rated being "ability to write and compose a business letter", a behaviour considered age appropriate to a normal 19 year old adult.

Similarly, self-motivation has already been discussed in the context of being an important defining factor in adaptive behaviour. However, the VABS does not distinguish between the person with schizophrenia suffering from apathy and volitional lack who will not "perform routine household tasks without being asked e.g. replace a fuse" and the person who has no electrical knowledge.



The VABS therefore provides functional information on individual performance that must be viewed as independent from ability. Consideration of this concept is essential in the further interpretation of the results of this study.

The schizophrenia group perform better than either one, or both other groups on all VABS domains and sub-domains. Without exception, performance to the upper limit of the normal range (table 26) is seen in at least one individual in each domain and sub-domain in the schizophrenia group. In learning disability and co-morbid subjects the upper end of the normal range is not attained for community domain scores, daily living skill domain scores or a variety of sub-domain scores. The issue of a ceiling effect occurring in the schizophrenia control group should therefore be borne in mind in the interpretation of results.

#### 11.4.2 Between group comparisons

The results for each domain and constituent sub-domains will be considered.

The total community domain is the one domain in which the schizophrenia group are clearly more able than either group with learning disability. This domain correlates significantly with Quick IQ, in both schizophrenia and co-morbid groups, and with the RBMT SP score in the learning disability and schizophrenia groups.

The correlations between IQ and total community scores in the co-morbid and schizophrenia groups are 0.455 and 0.529, respectively. These are consistent



with the observations of Reschley (1982), who described the usual range for correlations between adaptive behaviour and IQ as 0.4 -0.6. When the effect of IQ on the community domain scores is controlled for, by performing a partial correlation, the two RBMT SP score correlations are lost. Performance on this domain is therefore largely dependent upon intelligence, as determined by the Quick IQ test. Written and expressive language abilities are both integral to the overall community assessment.

All subject groups attain up to the maximum score in the receptive and expressive sub-domains, although a large degree of variance is seen in the performance of co-morbid groups in the former. At the upper limit of this sub-domain a 19 year old adult would be expected to “attend to a school or public lecture for more than 15 minutes”. People with psychiatric illness may find this difficult for reasons relating to psychopathology, whilst people with learning disability may have attention difficulties in this regard. This is evident when correlational data is considered (figure 28). All three symptom clusters of the PANSS and also current chlorpromazine equivalent are negatively correlated with the total community score in the schizophrenia group, but there are no negative correlations in the co-morbid group. The score on this domain is linked to measures of illness severity in the schizophrenia group, but not the co-morbid group. This may be because co-morbid people perform at a lower level than people with schizophrenia on this sub-domain and therefore impairments, other than psychopathology, preclude the majority from attaining a score in which psychopathology is influential (i.e. a floor effect occurs).

People with co-morbidity and learning disability perform to the same level of ability on the daily living skills domain. When the domestic sub-domain is considered the co-morbid group perform significantly worse than both other groups. Although performance on this domain is generally poor (it includes the ability to sew on buttons and perform a variety of chores) it is reasonable that performance correlates negatively with the amount of time the subject has spent in hospital. Many subjects who were institutionalised for a number of years may not have had the opportunity to perform some of these tasks. If this is the case, the VABS scoring manual awards an intermediate score. It is of note that the poor performance on this sub-domain does not correlate with the total number of days spent in hospital in the co-morbid group. This may be because many of these subjects, although living in the community, live in supported accommodation (chapter six).

Once again scores of the socialisation domain and sub-domains in people with schizophrenia negatively correlate with indicators of illness severity (all three psychopathology clusters and chlorpromazine equivalent). However, this is not the case in the co-morbid group who show more adaptive behaviour impairment in these areas than schizophrenia controls.

When the cumulative percentage graphs of the three domains are considered for each group (figures 12-14) the biggest discrepancy between scores (believed to be correlated to IQ) is seen for the total community domain (figure 12). The variance between groups is less marked in the daily living skills

domain (figure 13) and in the socialisation domain (figure 14), where group variance appears minimal. It seems therefore, that either schizophrenia controls are relatively more impaired on the socialisation domain, or that co-morbid and learning disability groups perform relatively better on this domain than others. Given that the total mean scores in all three groups are well below the upper possible limit the former explanation is more likely.

The performance on the total socialisation score in people with schizophrenia also correlates positively with Quick IQ test. Bowens and colleagues (1994) have established a link between cognitive dysfunction and poor social functioning, in terms of social skills, in people with schizophrenia. However, if this is the only explanation for low scores in the schizophrenia group, then the co-morbid group might also be expected to show a correlation between IQ and this domain, which is not evident.

In their review of measures of social skills in adaptive behaviour scales, Gresham and Elliot (1987) correctly indicate that the VABS incorporates some unconventional questions as part of the socialisation domain i.e. thoughtfulness, makes or buys a small gift on own initiative, keeps a secret for more than a day. Perhaps both of these tasks require the subject to have an intact 'theory of mind' (Premack and Woodruff, 1978; Baron-Cohen et al, 1985) ability. This alludes to an individual being able to predict correctly the wishes and intentions of others. It has been proposed that people with schizophrenia may have an impaired theory of mind ability and that this may contribute to the

formation of specific symptomatology (Frith, 1992). Lack of theory of mind ability has been shown to correlate with all three symptom clusters of the PANSS in people with schizophrenia, but no symptom clusters in people with co-morbidity (Doody et al, 1998). The results of this study, assuming elements of the socialisation sub-domain are comparable with theory of mind ability, concurs with these findings.

In a study to devise a cognitive battery to differentiate people with schizophrenia and “functional retardation” and schizophrenia and “developmental retardation”, Kay (1986) stated that it was possible to distinguish the two groups using the original Vineland Social Maturity Scales (Doll, 1953). This was done by comparison of social age, as rated by the scale, to comparative population norms. This work made the assumption that ‘a non-retarded schizophrenic, even if socially withdrawn can be expected to show social development on the scale’, the present study findings cast doubt on the validity of this assumption.

The learning disability control group show strong correlations with the negative symptom clusters of the PANSS in all three domains of the VABS, although the range of these symptoms in this group is limited (chapter six). Ratings of movement disorder, both Parkinsonian and dyskinetic are also strongly negatively correlated with performance in this group of unmedicated subjects. The presence of spontaneous involuntary movement disorders may render the practical performance of many of the tasks difficult or may stigmatise the

subject in social interactions and lead to social avoidance. Alternatively, movement disorders may be considered as a proxy for the degree of cerebral dysfunction that is present in these individuals.

#### 11.4.3 Gender specific issues

Significant gender differences between mean VABS scores occur in daily living skills and socialisation domains in the schizophrenia control group. No gender specific differences are seen in either the co-morbid or learning disability groups.

Sex differences in the domestic skills of daily living, which concur with the findings of this study, have also been found in people with schizophrenia by Sood and co-workers (1996). When groups of long stay institutionalised subjects were compared to long term community patients, men in the community performed better than male subjects resident in institutions, no between group differences existed in females.

Many of the VABS items in the domestic sub-domain are greatly influenced by cultural values and stereotypes. It may be quite acceptable for men not to be skilled in cooking, cleaning, sewing and other such domestic tasks in many cultures, where this is considered the role of women. Clearly a lack of ability in this domain may be an impediment to independent living in an individual. It is of little surprise that people with schizophrenia who do cope in a community setting have better domestic skills than those who remain institutionalised.

Nevertheless, it has been demonstrated that skills of cooking, cleaning and home maintenance may be nurtured in people resident in hospital with severe and enduring schizophrenia. The main requirement for success in such domestic rehabilitation is a suitable social training package with high staff-patient ratios (Hollander et al, 1981).

It is possible that sex differences in the daily living skills domain are not seen in people with learning disability, or co-morbidity, because cognitive impairment has been present since childhood in these individuals. Consequently, these skills have not been lost as a result of illness, but were simply never present.

In a similar way gender differences in socialisation skills may be said to exist in people with schizophrenia without any cognitive impairment because social skills have been acquired in these individuals to a degree, but then lost. This process of attrition of interpersonal skills is gender specific. It has been shown by others that women experience less of the adverse interpersonal psychosocial consequences of schizophrenia than men, even when both IQ and psychopathology are equivalent between groups, as is the case in the present study (Andia et al, 1995).

This is substantiated by consideration of VABS assessments in children. Normal children show higher overall scores than children who experienced meningitis in the first six months of life (Wald et al, 1985) and groups may be differentiated on the results of the VABS alone. Therefore, this implies that

children who had meningitis fail to acquire these skills relative to normal peers. By way of analogy, people in the co-morbid and learning disability groups may be considered as never having acquired these skills. Yet people in the schizophrenia group did acquire socialisation and daily living skills, but these have been modified by illness. This explains why such a strong negative correlation exists between conventional indices of disease severity in the schizophrenia group, but not in the co-morbid group.

### 11.5 Conclusions

The schizophrenia control group show relatively well preserved adaptive functioning, except within the socialisation domain. The impairment seen in this domain may be a reflection of specific theory of mind deficits, thought to occur in people with schizophrenia (Corcoran et al, 1995). Gender specific differences occur in daily living skills and socialisation domains in this group.

In contrast, the co-morbid group are severely impaired in all areas of adaptive functioning. Although unlike the schizophrenia control group, neither daily living skills nor socialisation are correlated with indices of disease severity i.e. days in hospital, psychopathology or chlorpromazine equivalent (all present at comparable levels in both groups – chapter six). It is suggested that many adaptive functions were never acquired by the co-morbid group, who have been severely impaired since childhood. Whereas in the schizophrenia control group adaptive behaviour, with the exception of interpersonal skills dependent

on theory of mind ability, have been learnt but subsequently modified by the course of illness. As these behaviours have never been present in the co-morbid group they are not influenced by psychopathology or medication. Paradoxically, the co-morbid group may actually be demonstrating evidence of a more severe form of schizophrenia than the schizophrenia control group. Such a model assumes that the inability to acquire adaptive functioning skills is the consequence of a process intrinsic to schizophrenia and not learning disability per se.

Although co-morbid subjects have more involuntary movement disorders than people with learning disabilities (chapter ten), no correlations with adaptive behaviour abilities are seen. It is suggested that the presence of spontaneous involuntary disorders of movement in the learning disability group may be a proxy for the severity of cerebral dysfunction present. This is not the case in either the co-morbid or schizophrenia groups, suggesting that a different mechanism compromises adaptive behaviour in people with schizophrenia.



## CHAPTER TWELVE

### FAMILY HISTORIES AND KARYOTYPIC ANALYSES OF THE STUDY

#### POPULATION

*"It also often occurs that among members of some families disorders of quite another kind appear, epilepsy, hysteria and manic depressive insanity."*

Kraepelin, 1919

#### 12.1 Introduction

##### 12.1.1. Mild learning disability, IQ and family histories

Following the discovery by Lejeune (1959), that Down's syndrome was the result of an extra chromosome 21, it was speculated that people with learning disabilities and congenital malformations were more likely to have detectable chromosomal abnormalities than those who display simple Mendelian modes of inheritance (Baraitser, 1986). In 1981, the aetiology of idiopathic mild learning disability was thought to untraceable in 55% of cases (Hagberg et al, 1981). Of those cases where aetiology could be determined, prenatal factors were involved in 33%, fetal alcohol syndrome was present in 8% and 5% were considered to be of genetic origin.

Lubs first demonstrated a fragile site on the X chromosome at Xq27 in 1969, this has subsequently been shown to occur in 1 in every 3000 live born males (Lubs et al, 1984). It is now believed to be one of the commonest causes of learning disability today.

Nichols (1984) studied the familiarity of idiopathic mild learning disability and concluded that the risk of recurrence in first degree relatives was between 13-33% and the risk in second degree relatives 5-9%. Some of these people may have had fragile X syndrome. A more recent study of children attending remedial education, with a diagnosis of mild idiopathic mental retardation, has provided evidence that between 20-25% of siblings also had idiopathic mild learning disability (Bundey et al, 1989). Children participating in this study were screened to exclude any contribution from fragile X sites.

It is often said that the contribution of 'sub-cultural' learning disability partially explains the skewed normal population IQ curve, where a relative excess of IQs between 50 and 70 are present. This 'sub-cultural' group comprises an excess of people from lower social classes, many of who have backgrounds of both emotional and financial deprivation.

In an English study, Lamont (1988) found that 56% of 169 children with mild learning disabilities were from social classes IV or V. Similarly, in a Scandinavian birth cohort of 12,000 children followed up until the age of 14, mild learning disability was found to be commoner in social classes III, IV and V (Rantakallio, 1987). The prevalence of mild learning disability in a Swedish suburban town has recently been determined to be 12.8/1000 (Fernell, 1996).

In stark contrast to these figures, the prevalence of mild learning disability in children living in Karachi in Pakistan, has been determined as 65.3/1000

(Durkin et al, 1998). This is much higher than prevalence estimates from the industrialised countries. A lack of maternal education was strongly associated with the presence of mild learning disability in Durkin et al's study, as was a history of perinatal difficulties. Indeed, a case controlled study of obstetric complications has reported that the introduction of specialised neonatal care units in medically advanced societies, has altered the risk of neonatal death to the risk of surviving with disability in many cases (Louhiala, 1995). So there are clearly many familial factors, which may be either environmentally or genetically mediated, that contribute to the aetiology of idiopathic mild learning disability, of which little is formally known.

In a review of all types of learning disability, Wahlstrom (1990) determined that a Mendelian autosomal dominant mode of inheritance could be determined in 41 conditions and an autosomal recessive mode of inheritance in 138. Furthermore, at this time 69 conditions associated with learning disability had been mapped to an autosome and 73 to the X chromosome (Thapar, 1992). The field of genetic mapping is advancing technically with such rapidity, that these figures are already obsolete.

#### 12.1.2. Schizophrenia, IQ and family histories.

A review of the many studies considering the possible genetic origins of schizophrenia is outwith the scope of this thesis. However, it has been firmly established by epidemiological methods that schizophrenia is a disease that

does aggregate in some families (Sham et al, 1994), although the mechanism by which this occurs remains elusive.

Twin studies (Gottesman and Shields, 1966), adoption studies (Kety et al, 1968), segregation analysis (Vogler et al, 1990), linkage analysis (St.Clair et al, 1990) and association studies (Sanders et al, 1991) have all been used to explore the genetics of schizophrenia (Kendler and Diehl, 1993).

The validity of many between group comparisons of 'familial' and 'sporadic' types of schizophrenia have been questioned on methodological grounds (Roy and Crowe, 1994). Many of the studies reviewed by these authors were limited by small sample sizes, inadequate diagnostic criteria of affected relatives, or poor definitions of sporadic and familial cases.

In a study of outcome in 342 subjects with schizophrenia, Johnstone et al (1995) found poor outcome was frequently associated with a paucity of information pertaining to family history. This was often as a consequence of family fragmentation. In epidemiological studies of people with mild learning disability, there also seems to be evidence of family fragmentation. In families where a child under 14 years of age has mild learning disability, both mother and father are more likely to have died, be unemployed, or to be receiving disability allowances, relative to the families of normal age matched controls (Rantakallio, 1987). The extent to which social class factors, or a family history of learning disability confounds this effect is unknown.

### 12.1.3 Karyotyping in people with schizophrenia and pre-morbid cognitive impairment.

Over the course of the last half a century, refinement of cytogenetic techniques have enabled the identification and characterisation of chromosomal abnormalities with increasingly higher levels of resolution. Tengström and Autio (1987) found 15 individual chromosomal abnormalities, using high banding resolution, in 89 subjects with mental retardation whose chromosomes had previously been reported as normal.

#### 12.1.3.1 Sex chromosome studies

Early studies focused on the identification of additional Y chromosomes in the genotype of people with learning disability and aggression (Jacobs et al, 1965). Subsequently, techniques became available to rapidly determine the number of X chromosomes present in metaphase cells. This led to several surveys of large institutionalised populations and the subsequent identification of residents with sex chromosome anomalies (SCAs; Price et al; 1976; Hunter et al, 1977). There appeared to be an excess of people with a diagnosis of schizophrenia amongst those found to have SCAs in these studies (DeLisi et al, 1994). In keeping with the expected phenotype of some SCAs (e.g. XXX, XXY) a number of these individuals also had co-morbid mild learning disability. These findings led to consideration being given to the possible role of the X chromosome in both neurodevelopment (Murphy et al, 1993; Reiss et al, 1995;

Skuse et al, 1997) and the psychoses (Crow and DeLisi, 1988; DeLisi et al, 1989).

#### 12.1.3.2 Chromosome 18.

In 1969, Ayraud and colleagues reported the case of a female affected by schizophrenia, deafness, multiple physical anomalies and mental retardation. When karyotypic analysis was performed she was found to have a deletion of the short arm of chromosome 18 (18p-). A case of paranoid schizophrenia in a woman of short stature with a speech impediment and a family history of autism, has also been reported to be associated with a deletion of the short arm of chromosome 18 (18p-) (De Marchi et al, 1995). This is now known to be the second most frequently occurring autosomal deletion and is not always associated with psychosis (Bassett, 1992). Nevertheless, a collaborative group from Scotland and Denmark (Mors et al, 1997), recently found a person with schizophrenia belonging to a multiply affected family to be a carrier of a chromosome 18 inversion (inv(18)(p11.3;q21.1)).

#### 12.1.3.3. Trisomy 8

In 1975, Sperber reported the occurrence of schizophrenia and an organic brain syndrome in a person with trisomy 8 (47,XX,8+). Subsequent reports of three cases of trisomy 8 found no evidence of psychotic illnesses in those affected (Gagliardi, 1978; Ioan et al, 1986). However, a case of schizophrenia has been reported in one individual with mosaic Klinefelter's syndrome and trisomy 8 (47,XXY/48,XXY,8+) (Ong and Robertson, 1995).

#### 12.1.3.4. Chromosome 5

Interest in chromosome 5 and schizophrenia was aroused by Bassett (1988) who found a co-segregation of a partial trisomy of chromosome 5 in a family with mildly dysmorphic features. Following this, Sherrington et al (1988) reported a positive finding for a susceptibility locus to schizophrenia on chromosome 5p. Interest in this area dwindled when linkage analysis of large Scottish families who were multiply affected with schizophrenia failed to replicate this (St.Clair et al, 1990) and a North American study failed to find any association in the 5p area with schizophrenia (Kennedy et al, 1988). Furthermore, a single case report of a subject with partial trisomy 5 and schizophrenia, the balanced translocation being inherited from one parent (Malaspina et al, 1992), did not show an overlap with the area of chromosome 5 associated with the family described by Bassett (1988).

#### 12.1.3.5 Chromosome 9

Another single case report describes a de novo interstitial deletion of chromosome 9 (9(q32q34.1)) in a man with dysmorphic features, including a soft palate abnormality, borderline learning disability (IQ 75) and schizophrenia (Park et al, 1991). There is also a reported case of a chromosome 9 abnormality, a pericentric inversion, associated with schizophrenia (Nanko, 1993), but this individual did not have a lowered IQ.

#### 12.1.3.6. Velo-cardio-facial syndrome.

In the last six years there have been several reports of the occurrence of psychotic illnesses in patients diagnosed as having velo-cardio-facial syndrome (VCFS) and their relatives (Shprintzen et al, 1992; Pulver et al, 1994a; Lindsay et al, 1995; Karayiorgou, et al, 1995; Gothelf et al, 1997).

VCFS (also termed Di George syndrome or Shprintzen syndrome) was first described in 1978 (Shprintzen et al, 1978). Since the characterisation of VCFS two decades ago a substantial scientific literature has developed on its genotypic features. It is an autosomal dominant condition with a prevalence of 1 / 4000 births and is associated with small chromosomal deletions in the q11 band of chromosome 22 (Kelly et al, 1993). In a small number of cases deletions may be present on the p13 and p14 bands of chromosome 10 (Daw et al, 1996).

The characteristic clinical features of the VCFS are; cleft palate, hypernasal speech, cardiac anomalies, hypocalcaemia, learning disability and characteristic facies (Goldberg et al, 1993).

In a study of 265 residents of learning disability hospital in Wales fluorescent *in situ* hybridisation (FISH) was conducted on a sample of 74 individuals who fulfilled criteria associated with the diagnosis of VCFS. 2 of these subjects (12% of all the subjects with mild learning disability) were demonstrated to have a previously undetected chromosome 22q11 deletion, both had the co-morbid conditions of mild learning disability and chronic schizophrenia (Murphy



et al, 1997). On the basis of their findings, Murphy and his colleagues suggest that any individual presenting with a history of mild learning disability, who subsequently develops schizophrenia, should be genetically screened for VCFS.

The region of chromosome 22 implicated in VCFS (22q11) has been further examined by *FisH* techniques. A human mitochondrial citrate transporter gene (SLC20A3) has been localised to band 22q11.21 (Stoffel et al, 1996) and a catechol-O-methyltransferase gene polymorphism has also been found in the area (Lachman et al, 1996). It has been hypothesised that this polymorphism may be associated with bipolar affective spectrum disorders, which have also been found to occur in association with VCFS (Papalos et al, 1996). Bipolar affective illnesses tend to occur more frequently in the minority of patients who have no deletions detected at 22q11 (Carlson et al, 1997).

A transmembrane protein gene maps directly to the deleted interval (and is therefore absent in VCFS) in 80-85% of patients (Sirotkin et al, 1997). This deleted gene normally encodes a protein of 219 amino acids which is found in large quantities in human adult lung, heart and skeletal muscle. It has been suggested as a possible candidate gene for psychosis.

## 12.2. Method

The family history method, as opposed to the family study method, was used to ascertain the family histories of subjects in this study (Andreasen et al, 1977). However, the Family History –Research Diagnostic Criteria instrument was not applied due to limited information in many cases. It is recognised that this may have resulted in under reporting and also be associated with false positives. However, it was uncertain at the time of planning the study if family members would be accessible for such in depth study. The time available to the author to conduct the full protocol was limited. It would not have been practicable to interview all ill relatives, due to time constraints.

A family tree was compiled for each subject. It has been demonstrated that this alone can improve the accuracy of the information obtained by family history taking by up to a factor of three (Baker et al, 1987). Information was derived from the case records and an interview with the subject in all cases. Where relatives were living and their whereabouts known, the subject was asked for permission for the author to make contact with the next of kin to substantiate and consolidate the family history. Relatives were interviewed face to face in all cases, no telephone interviews were conducted. Only one relative was contacted for each subject. It has been demonstrated that multiple interviews do not improve the accuracy of the family history method, which is generally of high specificity, but low sensitivity (Thompson et al, 1982). Enquiries were made regarding all first, second and third degree relatives. In particular any family histories of psychiatric or inheritable medical conditions were noted. Each family tree was scrutinised and evidence of schizophrenia or learning

disability, in any first or second degree relative sought. This information was then coded and entered into SPSS.

Between group differences in families histories of learning disability and schizophrenia were explored using Fisher's Exact Test. Within group differences in gender and epilepsy histories were also considered using Fisher's Exact Test. Co-segregation of clinical variables were considered in people with positive family histories of either learning disability or schizophrenia. Student's independent t-tests were used for continuous parametric data comparisons in subject groups that were split by family history groupings.

40mls of blood were taken from co-morbid subjects. 20mls were used for immediate karyotypic analysis and 20mls stored at -70°C to await later DNA extraction. The author did not conduct any of the laboratory work involved in this study. This was undertaken by the staff of the Medical Research Council (MRC) Human Genetics Unit in Edinburgh. Standard karyotypic analysis was conducted. Descriptive reports were obtained on all karyotyped samples.

Fluorescent *in situ* hybridisation (FISH) methods (Le Beau, 1996; Speicher et al, 1996) are now being conducted on all available samples with a probe paint set for the VCFS critical region of 22q11. This work continues to be ongoing at the time of writing.

### 12.3. Results

#### 12.3.1 Family history of schizophrenia

The results of the family history analysis between groups are depicted in figure 15. 20 (57%) of the 35 subjects in the co-morbid group, where a reliable family history was ascertained, have at least one first or second degree relative with a history of schizophrenia (figure 15). This compares to 12 (39%) of 31 subjects in the schizophrenia control group (Fisher's Exact Test two-tailed;  $p < 0.15$ ) and 2(9%) of 23 subjects in the learning disability control group (Fisher's Exact Test;  $p < 0.001$ ).

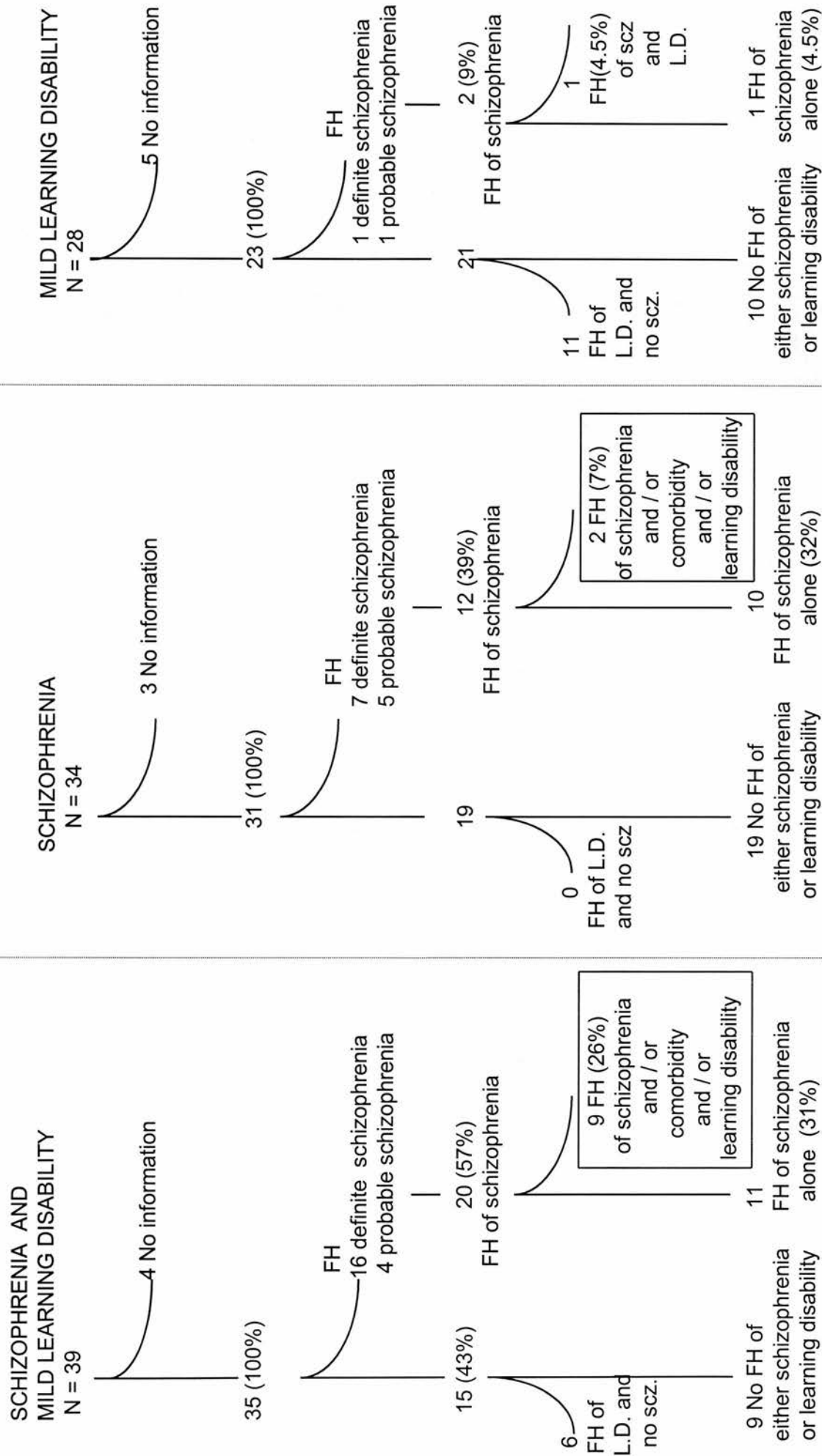
#### 12.3.2 Family history of learning disability

15 (43%) of 35 subjects in the co-morbid group have first or second degree relatives with learning disability (6 with learning disability alone and 9 from multiply affected families). This compares with 2 (7%) of 31 subjects in the schizophrenia control group (Fisher's Exact Test  $p = 0.001$ ) and 12 (53%) of 23 subjects in the learning disability control group (Fisher's Exact Test  $p = 0.59$ ).

#### 12.3.3 Family history of both learning disability and schizophrenia in different relatives (families are multiply affected)

In the co-morbid group 9 subjects (26% of the total number from whom a family history is available) are from multiply affected families in which first or second degree relatives (up to a maximum of 10) are affected by one of three conditions - schizophrenia and no learning disability, learning disability and no

FAMILY HISTORIES OF LEARNING DISABILITY OR SCHIZOPHRENIA IN FIRST OR SECOND DEGREE RELATIVES BY GROUP



schizophrenia, or schizophrenia and learning disability (the co-morbid state). This contrasts with only two subjects out of 31 (7%), with such family histories in the schizophrenia control group (Fisher's Exact Test  $p=0.049$ ), and one subject out of 23 (4.5%) in the learning disability group (Fisher's Exact Test  $p=0.07$ ).

When these multiply affected families are excluded from the analysis the percentage of subjects with a family history of schizophrenia alone in first and second degree relatives is remarkably constant between the co-morbid group and schizophrenia control group (31% and 32% respectively).

A highly significant difference is seen between subjects with no family history of either learning disability or schizophrenia in the co-morbid group (9/35) and the schizophrenia control group (19/31) (Fisher's Exact Test  $p=0.006$ ).

#### 12.3.4 Co-segregation of family history and clinical variables

For co-segregation data analysis each group of subjects was sub-divided into 5 categories, none of which were mutually exclusive. i.e.:-

1. Family history of multiply affected relatives (at least one relative with schizophrenia and others with either learning disability or co-morbidity).
2. Family history of schizophrenia alone and no learning disability or co-morbidity (SCZ alone).

3. Family history of any schizophrenia (includes those in multiply affected families)(SCZ any).
4. Family history of learning disability alone and no schizophrenia or co-morbidity (LD alone).
5. Family history of any learning disability (includes those in multiply affected families) (LD any).

The relative frequencies of people in these categories, by subject group are shown in table 29.

Table 29 - Relative frequencies of family history categories by subject group.

<u>FH</u> <u>CATEGORY</u>	<u>MILD L.D.</u> (N=23)		<u>CO-MORBIDITY</u> (N=35)		<u>SCHIZOPHRENIA</u> (N=31)	
	Positive	Negative	Positive	Negative	Positive	Negative
1. MULTIPLY AFFECTED	1	22	9*	26	2	29
2. SCZ ALONE	1	22	11^	24	10^	21
3. SCZ ANY	1	22	20^^	15	12^	19
4. LD ALONE	11**	12	6*	29	0	31
5. LD ANY	12**	11	15**	20	2	29

Fishers Exact Test

Significantly different to schizophrenia group:

Significantly different to mild learning disability group:

\*p<0.05

^p<0.05

\*\*p<0.01

^^p<0.01

Both the co-morbid and schizophrenia groups are significantly more likely to have a family history of schizophrenia than the learning disability group. Yet, both the learning disability group and co-morbid group are more likely to have a family history of learning disability than the schizophrenia group. Multiply affected families occur more commonly in the co-morbid group than the schizophrenia control group.

Fisher's Exact Test performed in both the co-morbid group and then the schizophrenia group did not show any significant differences when gender or history of epilepsy were considered for each family history sub-category. The five family history sub-categories were then each entered as the grouping variable in a Student's independent t-test between pairs of subject groups. This enabled exploration of the mean scores of other clinical variables, dependent upon whether a family history was present or absent.

The clinical variables that were entered into the analysis were: ages of first admission, consultation, diagnosis, symptomatology, neuroleptic, current chlorpromazine equivalent, time on depot medication, (co-morbid and schizophrenia groups only); NART score (schizophrenia group only); Quick IQ score, total positive, negative, general, PANSS scores, RBMT SP score, total NES score, total Waldrop weighted and unweighted scores, total DISCUS, AIMS, TAKE scores and total VABS domain scores. The significant findings of this analysis are shown in table 30 for each group and family history sub-category.



Table 30 – Significant co-segregations of positive family history sub-categories and clinical variables by group (Student's independent t-test).

<u>FH CATEGORY</u>	<u>MILD L.D.</u> (N=23) (Mean, s.d., p value)	<u>CO-MORBIDITY</u> (N=35) (Mean, s.d., p value)	<u>SCHIZOPHRENIA</u> (N=31) (Mean, s.d., p value)
POSITIVE FH OF MULTIPLY AFFECTED RELATIVES	(only one subject in positive FH group)	<b>Increased negative PANSS symptoms</b> (28.2, s.d.11.8 vs. 21.3, s.d.7.2: p=0.044)  <b>Increased TAKE total score</b> (8.1, s.d. 5.5. vs. 5.1, s.d. 2.8: p=0.042)	<b>Increased general PANSS symptoms score</b> (39.0, s.d.2.8. vs. 27.1, s.d. 7.4: p=0.035) (but only two subjects with multiply affected families in group)
<u>FH CATEGORY</u>	<u>MILD L.D.</u> (N=23) (Mean, s.d., p value)	<u>CO-MORBIDITY</u> (N=35) (Mean, s.d., p value)	<u>SCHIZOPHRENIA</u> (N=31) (Mean, s.d., p value)
POSITIVE FH OF SCZ ALONE	(only one subject with FH of schizophrenia alone)	NS	<b>Lower Waldrop scores. (less MPAs)</b> (weighted; 2.5, s.d. 1.7. vs. 4.4, s.d. 2.2: p=0.024) (unweighted, 2.7, 2.0 s.d. vs.4.7 , s.d. 2.5: p=0.04)
POSITIVE FH OF SCZ ANY	NS	NS	<b>Increased RBMT SP score (worse memory)</b> (20.4, s.d. 3.02 vs. 17.2, s.d. 4.4: p=0.034)
POSITIVE FH OF LD ALONE	NS	<b>Increased positive PANSS symptoms score</b> (16.8, s.d. 8.7 vs. 11.7, s.d. 4.6: p= 0.044) <b>Reduced total AIMS score (less dyskinesia)</b> (0.83, s.d. 0.98, vs. 3.39, s.d. 4.05: p= 0.045)	NS

POSITIVE FH OF LD ANY	NS	<b>Increased positive PANSS symptom score</b> (14.8, s.d.7.1 vs.10.9,s.d.3.7: p=0.04)	As for those with FH of multiply affected families. (same individuals)
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#### 12.3.5 Routine karyotypic analysis of the co-morbid group

Blood samples for karyotypic analysis were obtained from 29 subjects in the co-morbid group. Four of these subjects were found to have a chromosomal heterochromatic variant, three of these had a family history of schizophrenia in first or second degree relatives and one of these was from a multiply affected family, as described above. Two other subjects were found to have definite chromosomal abnormalities, one of these had a family history of schizophrenia.

Three G-band variants were found, they comprised additional, presumed satellite, material. One subject had 15ps+, another 21ps+, and a third had 21ps+ and 22ps+. The rates with which these variants occur are population dependent, however, reasonable estimates of their occurrence in the general population are; on chromosome 15, 3.1%, and on chromosome 21 and 22 around 2.5% for each (Lubs and Ruddle, 1970).

A fourth subject showed C band variants on both chromosomes 9 (9qh+ and inv9(p11q13)). The estimated frequency of 9qh+ in a Scottish newborn population is 0.5 - 7%, depending on size, and of total and partial inversions of chromosome 9 heterochromatin, 0.7% and 3.7% respectively (Buckton et al, 1976).

Two subjects had chromosomal abnormalities. The first has a complex re-arrangement involving a chromosome inversion and a balanced reciprocal translocation between chromosome 2 and 11. The karyotype of this subject is shown in figure 16. A metaphase stain is depicted in the upper portion of the photograph and the karyotype displayed beneath, the reciprocal translocation is clearly seen.

Fluorescent *in situ* hybridisation studies were used to complement standard G-banding methods to define and narrow the translocation breakpoints. The re-arrangement is complex, but has now been fully defined as  $\text{inv}(2)(\text{p15};\text{q13})\text{t}(2;11)(\text{q13};\text{q24.1})$ .

A *FisH* derived photograph of this re-arrangement is shown in figure 17. This shows a normal chromosome 2 at the 12 o'clock position with pink fluorescent staining present at the p arm (left) and the q arm telomere (right). Green fluorescent centromeric staining is also present. Below this chromosome and slightly to the left is the abnormal chromosome 11. This shows pink telomeric staining from the abnormal chromosome 2 portion attached to it. Finally, the abnormal chromosome 2 is seen at the bottom of the picture, just to the left of the 6 o'clock position. This shows the pink staining of the p arm and green centromeric staining, however the pink q arm telomeric staining, seen in the normal chromosome 2, is absent. This telomeric material has been translocated to the abnormal chromosome 11, where it can now be seen.

Figure 16 – Karyotype of  $\text{inv}(2)(\text{p15};\text{q13})\text{t}(2;11)(\text{q13};\text{q24.1})$

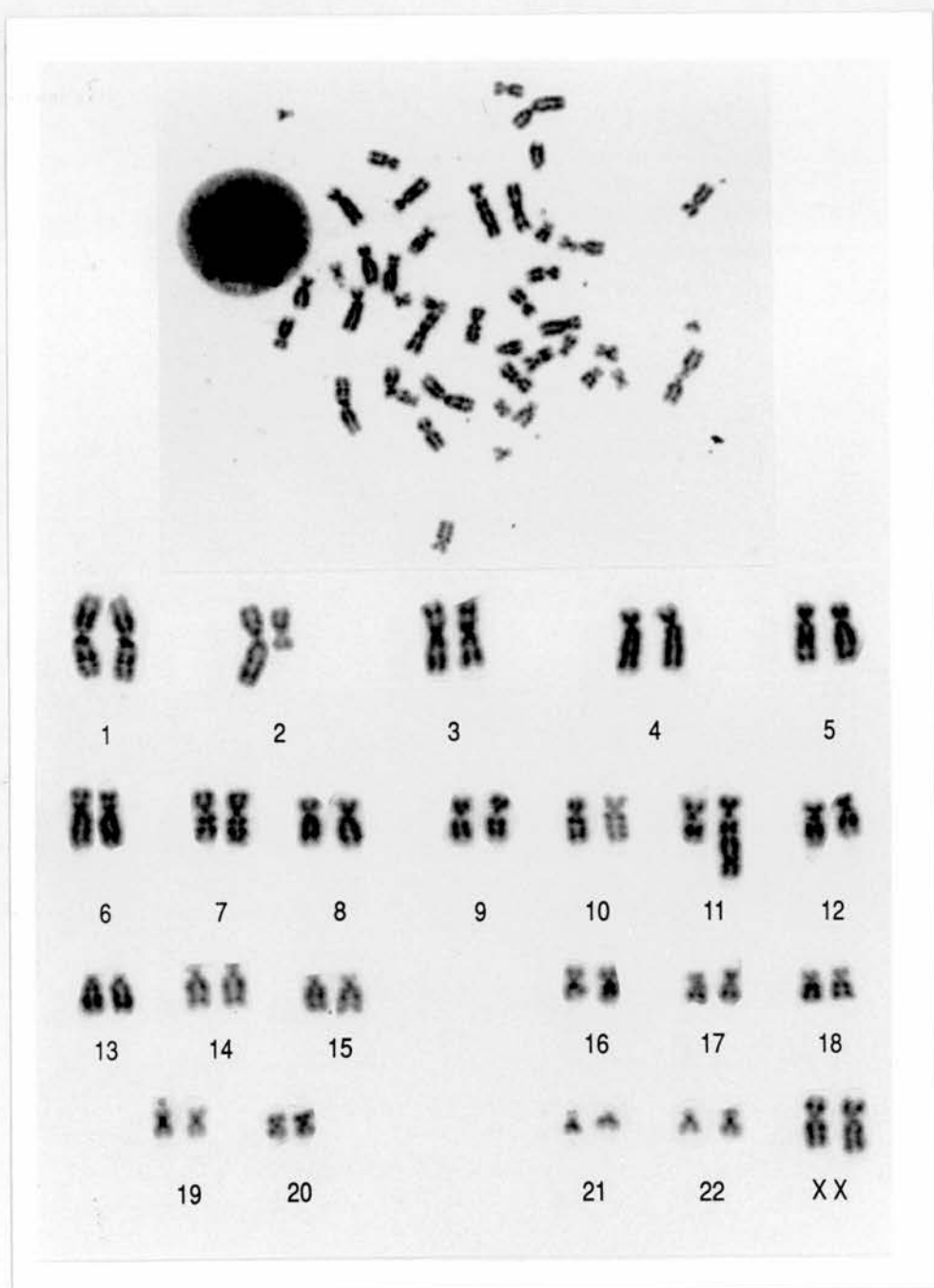
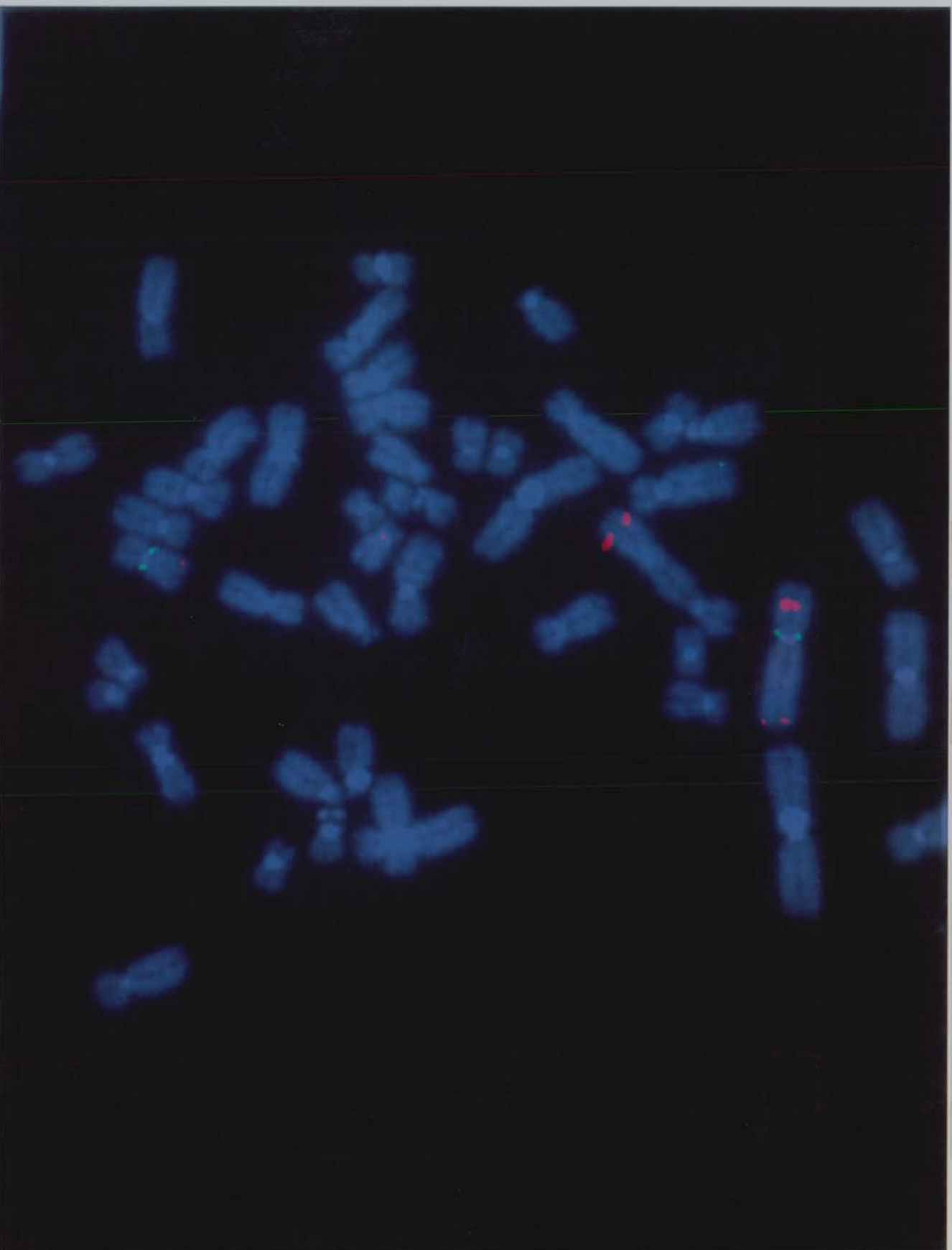


Figure 17 FISH study of inv(2) (p15;q13)t(2;11)(q13;q24.1)



This patient has a family history of schizophrenia. Reciprocal translocations occur in around 0.1% of the population.

The second subject has a sex chromosome abnormality, 47,XXX (Trisomy X Syndrome), the expected frequency of this occurring in newborn females is 1/1000. This subject does not have a family history of schizophrenia.

#### 12.3.6. FISH analysis using paint probe for 22q11 deletion

The blood samples obtained on 29 co-morbid subjects are currently being screened for deletions, as found in VCFS, using FISH with a paint probe for the 22q11 region. The results are not yet available.

### 12.4. Discussion

#### 12.4.1 A highly familial form of schizophrenia ?

In a population where information on the father's occupation is not available in nearly a third of cases, as is the case for the co-morbid and learning disability groups in this study, the validity of family history information must be questioned. In the collection of family history data in this study, every effort was made to obtain all available information.

The bias in the results from a lack of information would be to produce a false negative impression. The results in this study indicate an excess of family history in the co-morbid group, relative to the control groups. Information

obtained from the schizophrenia control group pertaining to family history tends to be more comprehensive, and is therefore more likely to provide information on positive family histories than the co-morbid group. It is unlikely that the co-morbid group results are biased to an over-representation of positive family histories, in fact the converse is more likely. The numbers of co-morbid subjects with positive family histories of either schizophrenia or learning disability should be regarded as an under estimate.

It could equally be assumed that because of the relatively high attrition rate of co-morbid subjects, those who did not participate may have fewer affected relatives, and that this has biased the sample. Once again, this seems unlikely, although there is no experimental evidence to consolidate this. Perhaps people with no family history of learning disability or schizophrenia are more likely to be cared for by well family members, come from less fragmented families, and therefore to be in relatively regular contact with health services and so be easier to recruit for research purposes.

Co-morbid subjects are more likely to have a family history of learning disability, or to come from multiply affected families than the schizophrenia control subjects. Kallman and colleagues (1941) found no increase in learning disability in the relatives of people with schizophrenia and no increase in schizophrenia in the relatives of people with learning disability, when compared to the normal population. At the time this was considered to be evidence that

the co-morbid state represented a chance co-occurrence of two distinct entities, as opposed to a separate condition with a hereditary component.

However, unlike the present study, probands with the co-morbid state were not selected in the 1941 study. The present study concurs with the work of Kallman when the family history of subjects with schizophrenia and subjects with mild learning disability are considered.

As stated above, the risk of recurrence of mild learning disability in the relatives of probands with idiopathic learning disability depends on social, environmental and genetic factors. In this study, 48% of people with idiopathic learning disability alone had a family history of learning disability and 43% of people with co-morbidity. These figures are not statistically different. However, there was no history of learning disability in the first or second degree relatives of any of the schizophrenia control subjects, this concurs with Kallman's work.

57% of the co-morbid group have a family history of schizophrenia in first or second degree relatives, compared to 39% of schizophrenia controls. These figures are not statistically different. However, people with learning disability have significantly less family history of schizophrenia, than either the schizophrenia control group, as Kallman demonstrated, or the co-morbid group.



Co-morbid subjects have the same amount of learning disability in their families as people with idiopathic mild learning disability alone, but also the same amount of schizophrenia as people with schizophrenia alone. They are therefore more likely to have multiply affected families. Kallman did not find this in his seminal study, as the co-morbid population was not included. Such positive exclusion of co-morbid subjects continues to be prevalent in many studies of schizophrenia today.

The results of the present study suggest that a highly familial form of schizophrenia may be occurring in the co-morbid group, the phenotypic appearance of which is variable in affected relatives.

#### 12.4.2 A highly familial form of schizophrenia of increased severity ?

It is hypothesised that three possible phenotypic expressions of 'schizophrenia' exist in people from multiply affected families. These are schizophrenia and no pre-morbid impairment, mild learning disability and co-morbidity, with the latter representing the most extreme form of the disease. Subjects with co-morbidity with a positive family history of either schizophrenia or learning disability, are therefore regarded as belonging to a multiply affected family when this hypothesis is applied.

People with co-morbidity from multiply affected families have a higher mean score of positive symptoms, negative symptoms and Parkinsonism (presumably due to an increased vulnerability to the effects of antipsychotics,

as discussed in chapter ten), but less dyskinesia, than people with co-morbidity, who are not from multiply affected families (table 30). Otherwise there are no differences between the two groups in terms of IQ, age of onset of psychosis, gender, history of epilepsy, overall RBMT memory function, NSS, MPAs, VABS scores or chlorpromazine equivalent doses of medication.

However, in the preceding chapters it has been reported that the co-morbid group have greater memory impairment (which correlates with NSS and MPA scores) and perform worse on 4 sub-domains of the VABS (receptive, expressive, domestic and play and leisure) than either control group. These effects can not be construed as the sequelae of concomitant epilepsy, as the learning disability control group contains equal numbers of people who have histories of epilepsy as the co-morbid index group.

Therefore 'sporadic' co-morbidity, i.e. where there is no family history of either learning disability or schizophrenia, is associated with fewer positive and negative PANSS symptoms, more dyskinetic movements, but less susceptibility to drug-induced Parkinsonism than 'familial' co-morbidity. Otherwise both co-morbid groups show more extreme deficits on a variety of measures than either control group.

By way of comparison, the schizophrenia control group shows no such effects of a family history of either learning disability, or schizophrenia on symptomatology or movement disorders. However, those people in this group

with a family history of schizophrenia have lower Waldrop scores (fewer MPAs), and more episodic memory deficits as determined by the RBMT SP score, than those with no family history. Otherwise there are no differences between the two groups in terms of IQ, age of onset of psychosis, gender, history of epilepsy, overall RBMT memory function, NSS, MPAs, VABS scores or chlorpromazine equivalent doses of medication. Hence, the corollary of these findings is that 'sporadic' cases of schizophrenia are associated with more MPAs and better memory functioning than 'familial' cases. Griffiths et al (1998) have also found fewer MPAs in people with no family history of schizophrenia, compared to those with a positive family history of the disease (chapter nine).

These findings are in keeping with the results of the Roscommon Family study of schizophrenia (Kendler, et al, 1996), where no relationships between age of onset of psychoses and familiarity were found. This has been replicated by Gorwood and colleagues (1995) in a large sample of 663 subjects with schizophrenia, although a slighter later age of onset in sporadic female cases was found by these authors. In contrast, a multi-centre international study of 1089 subjects with schizophrenia found sporadic cases to have a consistently higher average age of onset (Alda et al, 1996).

It remains unclear if, as seen in some medical and neuropsychiatric disorders, those with the greatest genetic propensity to develop schizophrenia do so at an earlier age. The results of the present investigation would tend to suggest that

this is not the case. Yet it does appear that the co-morbid group have a highly familial form of psychosis, which is more severe than schizophrenia occurring in people with no pre-morbid learning disability.

As such it is possible that the cognitive impairment first detected in early childhood, rather than the emergence of psychotic symptomatology in adolescence or early adulthood, is the first manifestation of the disease. This would also explain the lack of any finding of an earlier onset of psychosis in the co-morbid group, relative to the schizophrenia control group (chapter five). It is suggested that perhaps the co-morbid group show the first symptoms of the disease in a different cognitive format, at a significantly earlier age. This may be as a consequence of a high genetic propensity to develop this sub-type of the disease. It is tentatively suggested that these observations may be consistent with either an autosomal dominant mode of inheritance with variable gene expression, or a non-Mendelian anticipatory effect.

#### 12.4.3 Does anticipation occur in the co-morbid group ?

In the last 15 years genes with mutation-expansion triplet repeats have been found to be associated with fragile X syndrome (> 200 CCG repeats in the FMR1 gene), spinal and bulbar muscular atrophy, Huntington's disease (> 37 CAG repeats in the Huntington's gene), myotonic dystrophy (Ross et al, 1993) and autosomal dominant cerebellar ataxia (ADCA; Pujana et al, 1998). The biological basis of anticipation is unstable repeating trinucleotide expansions of DNA. Anticipation follows a non-Mendelian pattern of inheritance and the term

describes a pattern of disease progression within a pedigree. This is manifested by an earlier age of onset of the disease in successive generations, which is associated with a progressive increase in disease severity.

Evidence of anticipation may be sought clinically, by assessment of illness severity and age of onset within a pedigree. It may also be genetically determined by the 'repeat expansion detection' technique (RED technique; Schalling et al, 1991), which may be used to screen genomes for expansion sequences. Unfortunately, the RED technique does not localise trinucleotide repeats to any specific chromosome. It detects expansion repeats by molecular weight differentials and so simply indicates their quantitative presence and length.

In May 1994 two papers were published (Asherson et al, 1994; Bassett and Honer, 1994), which reported investigations of anticipation in schizophrenia. One was a clinical study of age of onset and disease severity in affected pedigrees (Bassett and Honer, 1994) which provided strong evidence for anticipation, the other a genetic study of anticipation in 29 multiply affected families which provided strong evidence against.

As Gorwood and colleagues have indicated (1996), there are a number of methodological problems in studies of anticipation in schizophrenia. Ascertainment biases may mimic anticipation As subjects from different generations are not interviewed at the same age, there is a greater chance of

finding a later age of onset in older generations, as they have been exposed to the risk of the illness for longer. In addition, the presence of an ill mother or father may increase the severity of illness for environmental, rather than true anticipatory reasons and also result in an earlier age of diagnosis assuming family contact with health professionals. A reduced fertility effect may also be seen to occur in early onset parents (Chotai et al, 1995).

Despite these difficulties, there have been many studies in the last four years in the area. The majority of clinical studies provide positive evidence for anticipation in schizophrenia (e.g. Thiabaut et al, 1995; Bassett and Husted, 1997; Ohara et al, 1997). Others have found evidence of anticipatory age effects, but not disease severity effects (i.e. Johnson et al, 1997), or no evidence of anticipation when potential sources of bias are controlled (i.e. Yaw et al, 1996).

Genetic studies using the RED technique have been similarly inconclusive. An association between schizophrenia and CAG and CTG repeats has been reported in both males and female subjects, but no clear causal relationship determined (O'Donovan et al, 1996). Anticipation has been reported in females with schizophrenia, for CAG repeat expansions (Morris et al, 1995). Other studies have shown no anticipation in either gender for CAG and CCG repeats (Ohara et al, 1997a). None of these studies have considered schizophrenia as it occurs in people with pre-morbid cognitive impairment.

Hereditary dentatorubral-pallidoluysian atrophy (DRPLA;) has been shown to be the result of an unstable CAG triplet repeat (Koide et al, 1994). It is an autosomal dominant disorder characterised by a wide variety of presentations including myoclonus, epilepsy, psychosis, cerebellar ataxia, choreoathetosis and dementia. Patients with an earlier onset tend to show larger expansions and progressive myoclonic epilepsy (Koide et al, 1994). Combinations of some of these features i.e. epilepsy, psychosis, movement disorders and cognitive impairment are found in the co-morbid group.

The CAG triplet in the human gene that causes DRPLA is called atrophin-1, or CTG-B37 and it is found on chromosome 12. Analysis of this gene from human brain tissue and blood leucocytes in people with schizophrenia shows only 7-22 CAG repeats, this is not enough to be regarded as pathological (Brando et al, 1996). In another study of peripheral leucocytes, no alleles with abnormal repeats at CTG B37 were found in people with schizophrenia or controls (Morris-Rosendahl et al, 1997). The median number of CAG repeats was 15, people with schizophrenia had significantly longer alleles than controls ( $p=0.002$ ), but these again were not considered pathological. No particular genotype was associated with schizophrenia. Neither of these studies considered people with schizophrenia and pre-morbid cognitive impairment.

Cardno and co-workers (1996) attempted to determine if the length of the CAG and CTG trinucleotide repeats, found to be associated with schizophrenia (O'Donovan et al, 1996) correlated with any clinical parameters. No significant



correlations were found with any OPCRIT variable ascertained by PSE-9 or SCAN interview and case note review, in a sample of 114 subjects with schizophrenia. Not all of the subjects had a positive family history. No neuropsychological assessments were conducted on these patients and their IQ is not reported. They were therefore a clinically heterogeneous group from which no significant clinical correlations could be expected. The authors' conclusion that the identification of the gene(s) that contain CAG and CTG repeats is not possible by reference to subsyndromes of schizophrenia as phenotypes is perhaps somewhat premature.

#### 12.4.4 Chromosomal variants.

In this study a high rate of chromosome variants are detected in co-morbid subjects with a family history of schizophrenia. Unfortunately, karyotyping was not routinely performed in the two control groups and so relative variant rates are unknown.

Reports in the literature do indicate that there are increases in chromosome variants in children with psychoses, where 4 variants were detected amongst 21 cases (Say et al, 1977), adults with schizophrenia (Judd and Brandkamp, 1967) and a 10% prevalence of chromosomal anomalies in institutionalised people with learning disabilities (Bourgeois et al, 1975). However, all these studies were performed prior to the advent of high resolution cytogenetic techniques and so the results are best regarded as conservative estimates. At the time it was believed that;



*"if genetic factors are present in the aetiology of schizophrenia, they cannot be elicited by current cytogenetic methods"*

(Judd and Brandkamp, 1967)

it is to be hoped that this is no longer true.

#### 12.4.5 Chromosomal abnormalities

DeLisi and Loretto found no autosome aberrations in a study of 45 men with schizophrenia (1990). Yet two chromosomal abnormalities were detected in co-morbid subjects in the present study, a complex re-arrangement involving an inversion and reciprocal translocation and a trisomy X syndrome.

The inv 2(p15;q13)t(2;11)(q13;q24.1) re-arrangement found in this study, in a co-morbid subject with a family history of psychosis, is of particular interest. There have been two other reports in the literature of schizophrenia in families which co-segregates, or partially co-segregates, with balanced translocations of chromosome 11 (t(1;11)(q43,q21); St.Clair et al, 1990 and t(6q14.2;11q25); Holland and Gosden, 1990). The breakpoint found in the re-arrangement in the present study is between these two i.e. q21-q25. A third report has identified a balanced translocation at t(6p22;11q22.3) which co-segregates with bipolar illnesses in an extended family (Smith et al, 1989).

In the first of these studies (St Clair et al, 1990), microdissection and microcloning of the breakpoint using *FisH* has been described (Muir et al, 1995). During identification of the breakpoint two polymorphic markers were identified, D1S1621 and D11S931. These enabled an allelic association study

to be performed in close proximity to the translocation breakpoint in individuals with schizophrenia, unipolar depression and a matched control group. No significant differences between allele frequencies were found in any of these three groups. Therefore, no evidence was provided, for a gene of major effect in the study population in this region (Wilson-Annan et al, 1997).

These reports have led to a great deal of interest in long arm of chromosome 11, which is regarded as a candidate region for genes associated with psychoses. This has been augmented by the finding that the D<sub>2</sub> dopamine receptor gene is located at 11q22-23 (Grandy et al, 1989).

Also nearby is the gene coding for porphobilinogen deaminase, a rate limiting enzyme in the haem synthetic pathway, mutations of which are believed to cause acute intermittent porphyria. However, no clinical co-segregation between major mental illness and acute intermittent porphyria has been found in families where the two conditions occur together (Patience et al, 1994).

Another gene known to be located in this area is a neural cell adhesion molecule, this is a glycoprotein on the surface of a cell which is involved neuronal cell to cell recognition during brain development. (Eubanks et al, 1992). It is possible that an encoding mutation in this gene may be associated with neurodevelopment changes that render an individual susceptible to the evolution of psychosis.

There have been a number of linkage studies looking at co-segregation with psychosis in multiply affected families in the 11q22 region and also alleles of the DRD2 gene. None to date have found a major gene effect in the region (Nanko et al, 1992; Wang et al, 1993; Su et al, 1993; Gill et al, 1993; Mulcrone et al, 1995; Kalsi et al, 1995). However, none have considered exclusively families where co-morbidity, schizophrenia and mild learning disability co-occur.

Triple X syndrome has been reported to be associated with schizophrenia (DeLisi et al, 1994). A report of two cases of schizophrenia associated with a triple X karyotype found no association with a positive family history of schizophrenia (Woodhouse et al, 1992). This is also the case in the subject identified in the present study. As discussed above, there is increasing interest in the literature regarding the role of the X chromosome in human brain development and the psychoses.

#### 12.4.6. The Velo-cardio-facial syndrome.

All of the co-morbid subjects in this study met at least two of the criteria for VCFS that Murphy and colleagues (1997) have suggested should indicate that the syndrome may be present. All subjects have both mild learning disability and schizophrenia. Many of the co-morbid subjects are also facially dysmorphic, show palatal abnormalities, as rated by the Waldrop scale, and have a family history of psychosis. These constitute a further three (of the

seven) VCFS criteria, the only two not specifically investigated by this study being hypocalcaemia and congenital heart disease

It is not clear, at present if the familial form of schizophrenia which seems to be occurring in the co-morbid group, is related to VCFS. *FISH* studies are in progress to determine this.

There have been many genetic linkage studies in multiply affected schizophrenia families in the 22q12-13 region. These followed a report (Pulver et al, 1994b) of a log of the odds score (lod score) for schizophrenia of 2.82 in the region, using an autosomal dominant model of inheritance. This is highly suggestive of linkage to psychosis and implies a gene of significant effect may be present in the region. Coon et al, (1994) found a lod score of 2.09, this time using a recessive model of inheritance. Subsequently, larger studies have found no evidence of linkage in this region (Polymeropoulos et al, 1994; Pulver et al, 1994c; Parsian et al, 1997; Hayakawa et al, 1998). Although interest in the area as a candidate region for schizophrenia, continues to be warranted (Vallada et al, 1995).

A human A2a adenosine receptor gene has recently been associated with the region 22q12-13. This gene encodes for one of the two receptors mediating the central effects of adenosine. It continues to be regarded as a candidate gene for schizophrenia, but has been excluded from the 22q11.2 region associated with deletions in VCFS (Deckert et al, 1997).

## 12.7 Conclusions

Co-morbid subjects have a tendency to belong to families where first and second degree relatives are multiply affected by three conditions; schizophrenia, mild learning disability and the co-morbid state. The co-morbid probands are as likely to have a family history of learning disability as people in the mild learning disability control group, and also as likely to have a family history of schizophrenia as people in the schizophrenia control group. Hence the observation of an excess of schizophrenia in people with mild learning disability has been experimentally confirmed. This pattern of familiarity does not support the premise that the occurrence of the two conditions, in the same individual, is due to chance alone.

Co-morbid subjects with relatives who have either schizophrenia, learning disability or the co-morbid state have an excess of both positive and negative symptoms relative to those with none. People with co-morbidity and a positive family history are more clinically unwell than those with none.

There is no evidence of an earlier age of psychotic symptomatology in the co-morbid group, with or without a family history, relative to the schizophrenia control group. This supports the view that co-morbidity may represent a severe form of schizophrenia. The onset of schizophrenia may have occurred in the co-morbid group in early childhood, at or before the time of detection of cognitive impairment .

In such a severe form of the illness it is hypothesised that cognitive impairment which is intrinsic to the schizophrenia process, is apparent prior to detectable psychotic phenomenology. Formal symptoms of psychosis are often difficult to detect in childhood, due to an inability to communicate and think in abstract terms. This may also be the case for people who are cognitively impaired from childhood.

The existence of a form of schizophrenia, of variable phenotypic severity, occurring in multiply affected families suggests the possibility of an anticipatory mode of inheritance. This is an area that has recently provoked both interest and controversy amongst schizophrenia researchers, but none have considered its particular applicability to the co-morbid group. Further systematised clinical and genetic studies of both co-morbid probands and their relatives, in the multiply affected pedigrees identified are necessary to investigate this possibility further.

If co-morbidity is a highly familial severe form of schizophrenia it may provide clues as to the aetiology of the generality of the condition. This study has shown that co-morbidity is associated with a higher rate of chromosomal variants than would be expected in the normal population. However, lack of information on the incidence of chromosomal variants in the control groups limits the interpretation of these results.

The finding of a co-morbid subject with triple X syndrome in this study serves to highlight the association between neurodevelopment and the X chromosome. However, the discovery of a complex chromosomal re-arrangement involving chromosomes 2 and 22 in a subject with a positive family history of psychosis, is of particular significance. The breakpoint region of chromosome 22 in this subject has been identified as a possible candidate region for a gene associated with schizophrenia by other researchers. Negative linkage reports are available for regions adjacent to this breakpoint, but specific markers of the region have not yet been developed. Hence, linkage studies have not been specifically conducted in the multiply affected families in which co-morbidity, schizophrenia and learning disability occur.

## CHAPTER THIRTEEN

### CONCLUSIONS:

#### BROADENING THE CONCEPT OF SCHIZOPHRENIA

*"The frequency of the defective or poor endowment will from this standpoint, so far as it is characteristic of dementia praecox, be capable of being regarded at least partly as an expression of engrafted hebephrenia, modified to a certain extent, as the first still indefinite action of the same morbid process which later causes dementia praecox."*

#### 13.1 A highly familial and severe form of schizophrenia

This study has shown that it is no longer valid to accept the conclusions of Hucker and colleagues from the 1979 study of people with co-morbidity that ;

*'there was no evidence to suggest that associated cerebral damage, perceptual defects or chromosomal abnormalities played any part in the aetiology of the psychoses in the co-morbid group'.*

Hucker et al, 1979

This thesis has provided evidence that people with pre-morbid cognitive impairment who subsequently develop schizophrenia have an illness which is qualitatively similar to schizophrenia in terms of psychopathology, memory impairment, MPAs, NSS, involuntary movement disorders and family history of schizophrenia. However, the presentation is quantitatively different from that of individuals with schizophrenia and no pre-morbid cognitive impairment in several aspects e.g. more negative symptoms, more memory impairment, more adaptive behaviour impairment and a greater likelihood of having a family history, not only of schizophrenia but also of mild learning disability. This supports the concept that schizophrenia in people with pre-morbid mild



learning disability represents a severe form of the disease. Co-morbid subjects are also dissimilar to people with mild learning disability alone in many respects.

The occurrence of multiply affected families in the co-morbid group and the incidence of both learning disability and schizophrenia in relatives of co-morbid probands, suggests this severe form of schizophrenia is highly familial. Karyotypic studies of the co-morbid population show a greater than expected number of chromosome variants and chromosomal abnormalities indicating that this familiarity is likely to have a genetic, as opposed to an environmental origin.

It is therefore proposed that schizophrenia, as it occurs in people with pre-morbid mild learning disability does represent a particularly severe form of the disease. This is qualitatively similar to schizophrenia in the normal population, but quantitatively greater impairment is evident on a variety of measures. Furthermore, there is evidence that this severe form of schizophrenia is highly familial and, in some cases, likely to be of a genetic aetiology.

### 13.2. A neurodevelopmental perspective.

The concept that the sequelae of any neurodevelopment insult are variable dependent on the timing and severity of the insult has already been explored (Chapter nine; Murphy and Owen, 1991). A mild insult, of a transient nature,

occurring early in development may be associated with less subsequent cerebral impairment than a severe insult, of an enduring nature, that occurs later in development.

In the first type of insult, little or no cognitive impairment may be evident in childhood, however in early adulthood psychosis may become apparent. In more severe forms of insult the degree of cerebral dysfunction will be more severe, resulting in global impairment from an early age and the development of psychosis in early adulthood. As the extent of neuropathology (macro or micro) is more severe in this second type of insult, epilepsy may be expected to occur in these cases with greater frequency than in cases associated with lesser degrees of dysfunction. Localised epilepsy e.g. temporal lobe, may indicate the site of the most extensively affected brain areas.

It is therefore suggested that pre-morbid cognitive impairment in people who later develop schizophrenia, may be intrinsic to the disease process. These people may be those who are exposed to neurodevelopmental insults that are severe, enduring or occur later in development. People who develop schizophrenia against the background of a normal or slightly reduced level of cognitive functioning may be those who have experienced relatively mild, transient or early neurodevelopmental insults.

These two types of insult may arise from either genetic origins e.g. mutation in a fetal neurodevelopment gene, or environmental origins e.g. maternal illness

or neonatal infection (meningitis / encephalitis). It is suggested that in co-morbid patients later, enduring or severe insults produce a more severe form of the disease that is manifested by cognitive impairment in early childhood prior to the development of psychosis

### 13.3.Epidemiological considerations

It has been established that in people with learning disability the risk of recurrence in relatives is dependent on both environmental and genetic factors. The recurrence risk of schizophrenia in relatives is also variable, although the determinants are less clearly defined. Schizophrenia incidence figures throughout the world are believed to be relatively geographically stable (Jablensky and Sartorius, 1988). However, people with co-morbidity are generally excluded from these epidemiological studies.

If co-morbidity does represent a severe and sometimes highly familial form of schizophrenia, as the results of this study tend to suggest, it is possible that our present concept of schizophrenia is too rigid. If co-morbidity is to be considered part of the schizophrenia spectrum, it perhaps represents one extreme in which cognitive impairment in childhood is the first manifestation of the disease.

The incidence of schizophrenia would therefore be greater than is currently believed. It is possible that other people with greater degrees of learning

disability may also be suffering from schizophrenia, but lack the communication skills to express the psychotic symptomatology which we associate with the disease.

'Sub-cultural' learning disability is often associated with social deprivation and fragmentation of family structure. If a severe form of schizophrenia contributes to the aetiology of mild learning disability, then major differences in the socio-economic classes of people affected by schizophrenia may be seen. People with co-morbidity in this study are predominantly from lower socio-economic classes relative to schizophrenia controls.

If a severe neurodevelopmental insult is causally associated with co-morbidity, then the comparatively good prognosis of schizophrenia in third world countries (Sartorius et al, 1986), may be attributed to the fact that people with potentially the most severe forms of the disease, often fail to survive into adulthood. This could be the result of rudimentary obstetric care, poorly controlled epilepsy, neonatal and childhood deaths from infections, malnutrition or other conditions that might be readily treated or avoided in developed countries.

#### 13.4 Future directions

Many studies of schizophrenia today preferentially exclude people with learning disability. Although it remains true that the inclusion of such people in studies of the generality of schizophrenia can produce skewed results, as this study

has shown, there is a need for this subtype to be included, perhaps with separate statistical analysis. Standard research practice may have caused the most severe cases of schizophrenia to be positively excluded from many studies. Such ascertainment bias may have restricted our understanding of the concept of schizophrenia, the true syndrome being clinically more diverse than previously believed.

Future clinical and genetic studies of multiply affected pedigrees of co-morbid probands may be of importance in determining the mode of inheritance in these families. It is possible that such further study of this potentially homogeneous group of individuals may reveal important clues as to the biological aetiology of the generality of schizophrenia.

Greater knowledge of schizophrenia, as it occurs in people with pre-morbid cognitive impairment, may also enable earlier identification of the illness i.e. prior to the onset of psychotic symptoms, by recognition of a specific pattern of biological and psychological impairment. This may lead to new strategies for treatment, intervention and ultimately prevention of the disease.

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## **ABBREVIATIONS**

AIMS	Abnormal Involuntary Movement Scale
APA	American Psychiatric Association
CI	Confidence Interval
CPZ	Chlorpromazine
DISCUS	Dyskinetic Identification System - Condenser User Version.
DRPLA	Dentatorubral-pallidoluysian atrophy
F.H.	Family History
IQ	Intelligence Quotient
LSD	Least Significant Difference Test
L.D.	Learning Disability
MPAs	Minor Physical Anomalies
NART	National Adult Reading Test
NES	Neurological Evaluation Score
NS	Not statistically significant
NSS	Neurological "Soft" Signs
PANSS	Positive and Negative Symptom Scale
RBMT	Rivermead Behavioural Memory Test
RBMT SPS	Rivermead Behavioural Memory Test Standardised Profile score
RM Screen	Rivermead Behavioural Memory Screening score.
SADS-L	Schizophrenia and Affective Disorder Schedule - Lifetime version
SCAs	Sex Chromosome Anomalies
SCZ.	Schizophrenia

RED	Repeat Expansion Detection (technique)
TAKE	Targeting Abnormal Effects Scale
VABS	Vineland Adaptive Behaviour Scale
VCFS	Velo-Cardio-Facial Syndrome

## APPENDIX ONE

### GENERAL HISTORY QUESTIONNAIRE

R.NO.

LEVEL OF PARTICIPATION	1 SEEN
	2 REFUSED
	3 LOST BUT NOTES TO 1990

SEX	1 MALE
	2 FEMALE

NATIONALITY	1 SCOTTISH	<u>ETHNICITY</u>
	2 ENGLISH	1 WHITE
	3 WELSH	2 BLACK
	4 EUROPEAN	3 WHITE/
	5 ASIAN	BLACK
	6 AFRO-CARIBBEAN	4 OTHER
	7 OTHER	

AGE

MARITAL STATUS	1 MARRIED
	2 SINGLE
	3 WIDOWED
	4 DIVORCED
	5 SEPARATED
	6 CO-HABITING

S-E GROUP	1	2	3	4	5
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LIVING CIRCUMSTANCES	1 ALONE
	2 SPOUSE / COHABITEE
	3 RELATIVE
	4 SUPPORTED (NOT 24HR)
	5 SUPPORTED (24HR)
	6 LONG TERM CARE

IF LONG TERM CARE:	
LENGTH OF TIME IN CARE	1 <1 YEAR
	2 1-2 YEARS
	3 2-5 YEARS
	4 5-10 YEARS
	5 >10 YEARS

TYPE OF HOSPITAL	1 PSYCHIATRIC
	2 LEARNING DISABILITY

CURRENT SERVICE UTILISATION (TIME OF INTERVIEW)

INPATIENT	1	NO
	2	YES

PSYCHIATRIC OUTPATIENT

CPN

G.P.

PRACTICE NURSE

SOCIAL WORKER

DAY HOSPITAL

DAY CENTRE

ATC

VOL. AGENCY

HOME HELP

OTHER

CODING OF FREQUENCY:

0	NONE
1	FREQ.NK
2	DAILY
3	2 - 4 DAYS WEEK
4	WEEKLY
5	FORTNIGHTLY
6	MONTHLY
7	OTHER

UNDER MHA CURRENTLY	1	NO
	2	YES

AGE FIRST SYMPTOMS

AGE AT DIAGNOSIS OF SCZ

AGE FIRST CONSULTATION

AGE FIRST ADMISSION

NUMBER OF ADMISSIONS	TOTAL
	PSYCHIATRIC HOSPITAL
	L.D. HOSPITAL

TOTAL TIME IN HOSPITAL	0	No information
	1	Never hospitalised
	2	<3/12
	3	<6/12

	4	<1 year
	5	<2 years
	6	<5 years
	7	>=5 years
OUTPATIENT TREATMENT	0	No information
	1	No contact
	2	Brief contact
	3	>6/12 or several brief
	4	continuous for numerous years or many brief.

SPECIAL HOSPITAL DURATION OF STAY

IPCU DURATION OF STAY

# MEDICATION

<u>NEUROLEPTICS</u>	ALIPHATIC	PIPERIDINE
	PIPERAZINE	THIOXANTHINE
	BUTYROPHENONE	DIPHENYLBUTYLPYPERIDINE
	DIBENZOXAZEPINE	CLOZAPINE
	RISPERIDONE	

AGE FIRST NEUROLEPTIC

NEUROLEPTIC FREE PERIOD

DEPOT DURATION	CURRENTLY ON DEPOT	1	NO
		2	YES

PRESENT CPZ EQUIVALENT

ANTICHOLINERGIC	CURRENT	1	NO
		2	YES
	DURATION		
BENZODIAZEPINE	CURRENT	1	NO
		2	YES
	DURATION		

LITHIUM	CURRENT	1	NO
		2	YES
	DURATION		
ANTIDEPRESSANT	CURRENT	1	NO
		2	YES
	DURATION		
ANTICONVULSANT	CURRENT	1	NO
		2	YES
	DURATION		
OTHER	CURRENT	1	NO
		2	YES
	DURATION		
ECT		1	NO
		2	YES

NUMBER OF ECT TREATMENTS (TOTAL)

NUMBER OF ECT COURSES

#### PAST MEDICAL HISTORY

NO. HOSPITAL ADMISSIONS

<u>OPERATIONS</u>	EYES	EARS	GUT	LIMBS
	BRAIN	GYNAE	OTHER	

<u>INVESTIGATIONS</u>	EYES	EARS	GUT	LIMBS
	BRAIN	GYNAE	OTHER	

HEAD INJURY	0	
	1	MILD NO LOC
	2	HOSPITAL NO LOC
	3	LOC <10MINS
	4	LOC <30 MINS
	5	LOC <1 HOUR

	6	LOC <24 HOURS
	7	LOC >24 HOURS
ENCEPHALITIS	1	NO
	2	YES
MENINGITIS	1	NO
	2	YES
<u>EPILEPSY</u>	1	NO
	2	YES
AGE AT ONSET		
NATURE	1	TONIC-CLONIC
	2	MYOCLONIC
	3	ATONIC
	4	ABSENCE
	5	SIMPLE PARTIAL
	6	COMPLEX PARTIAL
	7	PARTIAL WITH SECONDARY
GENERALISATION	8	OTHER
NUMBER EVER	1	1-5
	2	5-10
	3	10-20
	4	20-50
	5	50+
CAUSE	1	IDIOPATHIC
	2	FEBRILE CONVULSIONS
	3	TRAUMA
	4	MEDICATION
FREQUENCY NOW	1	DAILY
	2	> 2 PER WEEK
	3	WEEKLY
	4	2-4 PER MONTH
	5	MONTHLY
	6	<12 PER YEAR
	7	YEARLY
	8	>YEARLY
	9	NONE FOR > FIVE YEARS
EEG EVER	0	NONE

(HIERARCHICAL)	1	NAD
	2	DIFFUSE CHANGES
	3	CLEAR EPILEPTIFORM ACTIVITY
	4	LOCALISED TO SPECIFIC AREA

IF EEG LOCALISED:	0	NONE
	1	TEMPORAL
	2	FRONTAL
	3	PARIETAL
	4	OCCIPITAL

EEG LATERALISATION	0	NONE
	1	LEFT
	2	RIGHT
	3	NEITHER

### EDUCATION

NORMAL SCHOOL (YEARS)

SPECIAL SCHOOL (YEARS)

EMPLOYMENT RECORD	0	No information
	1	No time off work
	2	Few days off work
	3	up to 6/12 off
	4	up to 1 year off
	5	up to 2 years off
	6	up to 3 years off
	7	up to 4 years off
	8	up to 5 years off
	9	Not worked in last 5 years due to illness

LONGEST EVER PERIOD IN ONE JOB (MONTHS)

### FORENSIC HISTORY

NO. OF POLICE CONTACTS

NO. OF OFFENCES

B.O.P.	THEFT	SHOPLIFTING
ASSAULT	EXHIBITIONISM	



HOMICIDE

OTHER

CUSTODIAL SENTENCE (NON SPECIAL HOSPITAL)

NUMBER

DURATION

NO. PSYCHIATRIC COURT REPORTS

NO. PSYCHIATRIC COURT REPORTS WITH  
SPECIFIC RECOMMENDATIONS

DRUG ABUSE

DEGREE OF ABUSE	0	No information or unclear
	1	Not at all
	2	Clinically insignificant
	3	Minor interference of normal functioning
	4	Important life modifications
	5	Major changes in life
	6	Major disruption of life

AGE WHEN BEGAN

AGE WHEN STOPPED

NARCOTICS	1	NO
	2	YES
AMPHETAMINE LIKE	1	NO
	2	YES
COCAINE	1	NO
	2	YES
SED\HYP\TRANQ.	1	NO
	2	YES
CANNABIS	1	NO
	2	YES
HALLUCINOGENS	1	NO
	2	YES
SOLVENTS	1	NO
	2	YES
CURRENT PROBLEM	1	NO
	2	YES

ALCOHOL

UNITS \ WEEK

CIGARETTES

NO. \ DAY

SELF HARM

NUMBER SUICIDE ATTEMPTS

GREATEST EVER SUICIDE INTENT	0	No information or unclear
	1	No intent / manipulative
	2	Minimal or unsure
	3	Definite but ambivalent
	4	Serious
	5	Very serious
	6	Extreme

GREATEST EVER MEDICAL THREAT	0	No information or unclear
	1	No danger (never took)
	2	Minimal (small scratch)
	3	Mild (10 aspirins)
	4	Moderate (10 seconal)
	5	Severe (cut throat)
	6	Extreme (careful plans every expectation of death)

SADS-L	1
	2
	3

1	SCHIZOPHRENIA
2	MDD
3	MINOR DD
4	B.P.I
5	B.P.II
6	ALCOHOL DEPENDENCY
7	DRUG DEPENDENCY
8	PANIC DISORDER
9	GENERALISED ANXIETY DISORDER
10	OBSESSIVE COMPULSIVE DISORDER
11	PHOBIA
12	OTHER

CLINICAL PSYCHOLOGY

YEAR	I.Q.
------	------

YEAR	I.Q.
------	------

YEAR	I.Q.
------	------

YEAR

I.Q

YEAR

I.Q.

CT SCAN

0

NONE

1

NAD

2

ENLARGED VENTRICLES

3

OTHER

KARYOTYPE

1

NO

2

YES

## APPENDIX TWO

### Dyskinesia Identification System : Condenser User Scale (DISCUS) (Sprague et al, 1989)

0 = absent  
1 = minimal  
2 = mild  
3 = moderate  
4 = severe

#### FACIAL

1. Tics	0	1	2	3	4
2. Grimaces	0	1	2	3	4

#### OCULAR

3. Blinking	0	1	2	3	4
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#### ORAL

4. Chewing / Lip Smacking	0	1	2	3	4
5. Puckering / Sucking / Thrusting Lower Lip	0	1	2	3	4

#### LINGUAL

6. Tongue Thrusts	0	1	2	3	4
7. Tonic Tongue	0	1	2	3	4
8. Tongue Tremor	0	1	2	3	4
9. Athetoid / Myokymic / Lateral Tongue	0	1	2	3	4

#### HEAD / NECK / TRUNK

10. Retrocollis / Torticollis	0	1	2	3	4
11. Shoulder / Hip Torsion	0	1	2	3	4

#### UPPER LIMB

12. Athetoid / Myokymic Finger-	0	1	2	3	4
13. Wrist - Arm ( not Tremor)	0	1	2	3	4

#### LOWER LIMB

14. Ankle Flexion / Foot Tapping	0	1	2	3	4
15. Toe Movement	0	1	2	3	4